LE CURE ONCOLOGICHE DOMICILIARI

Il contributo di ANT da 45 anni a casa di chi soffre

Sabato 10 giugno 2023

Centro Congressi FICO Eataly World Bologna
Via Paolo Canali, 8 - 40127 Bologna

FONDAZIONE 45 ANT FRANCO PANNUTI

LE CURE ONCOLOGICHE DOMICILIARI

Il contributo di ANT da 45 anni a casa di chi soffre

Farmacologia clinica del dolore. La base di oggi sulla quale costruire il domani

Romano Danesi - Prof. Ordinario Farmacologia
Università di Pisa

FONDAZIONE 45 ANT FRANCO PANNUTI

Disclosures of Romano Danesi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MSD			X		X		
Eisai			X		X	X	
AstraZeneca	X		X		X	X	
BeiGene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				

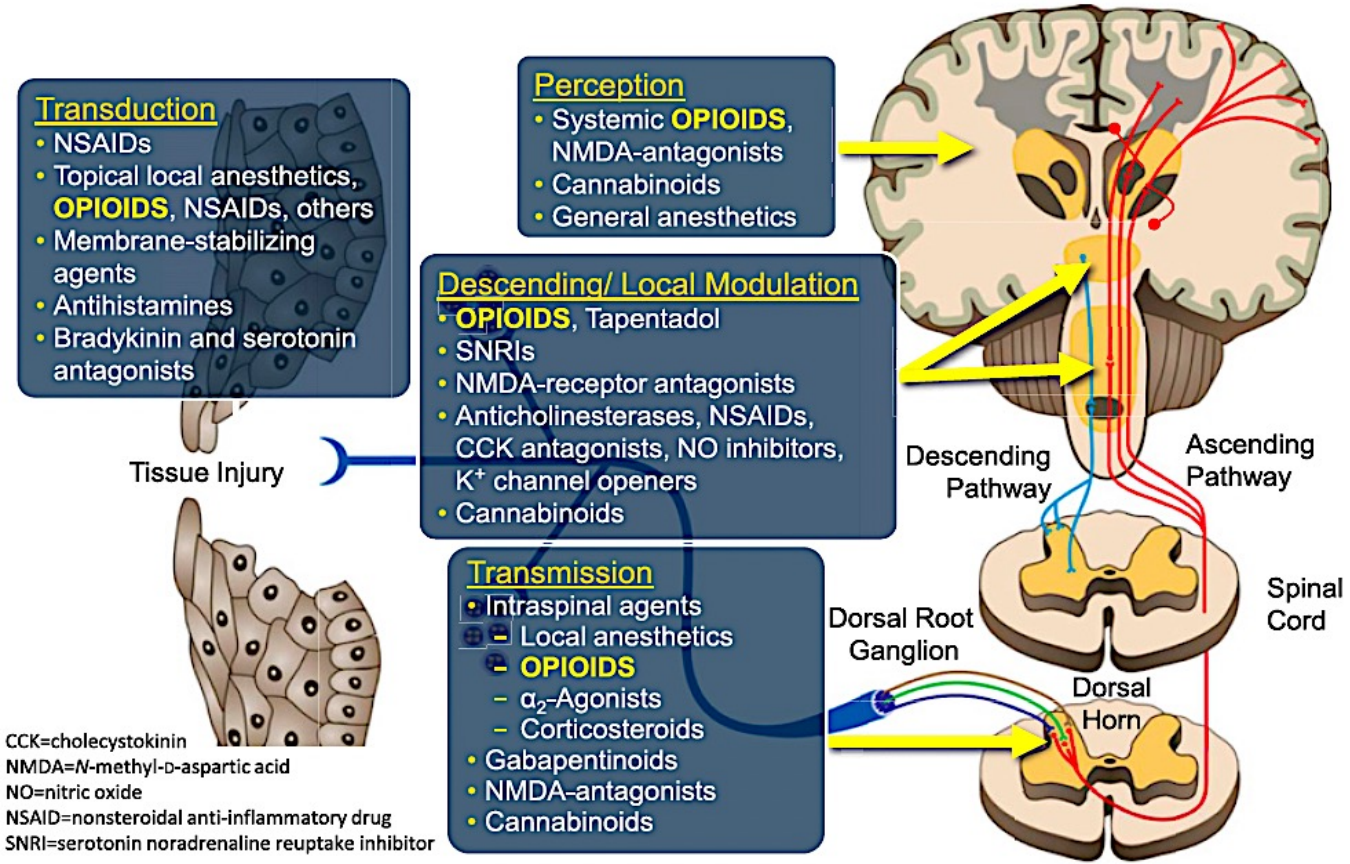
Pharmacological strategies to improve the treatment of pain

New cellular targets – new drugs on the horizon

Better management – drug-drug interactions

Improved diagnostics – pharmacogenetics

The sites of action of broad-spectrum analgesics



Gudin J. Journal of Pain and Symptom Management http://dx.doi.org/10.1016/j.jpainsymman.2012.08.013

Capturing novel non-opioid pain targets

What the analgesic targets do and where do they act?

Activity	Nervous System Region Affected	Successful Targets	Unsuccessful Targets
Decrease Inflammation	Peripheral	COX-2, SPR	CCR2, p38
Reduce Nociceptor Activation	Peripheral	NGF, P2X, AT2R	TRPV1
Reduce Excitability	Peripheral	VGSC, Nav1.8	Nav1.7, Kv7
Increase Inhibition	Central	MOR, KOR, SNRI, GABA	
Reduce Synaptic Transmission	Central	NMDAR, A2D, Cav2.2, CGRP	NK1, Cav3.2

A2D, alpha-2D–adrenergic receptor; AT2R, angiotensin II type 2 receptor; Cav, voltage-gated calcium channel; CCR2, C-C chemokine receptor type 2; CGRP, calcitonin gene-related peptide; COX-2, cyclooxygenase 2; GABA, gamma-aminobutyric acid; KOR, kappa opioid receptor; Kv7, voltage-gated potassium channel 7; MOR, mu opioid receptor; Nav, voltage-gated sodium receptor; NGF, nerve growth factor; NK1, neurokinin 1; NMDAR, *N*-methyl-D-aspartate receptor; P2X, purinergic receptor type 2X; p38, protein 38; SNRI, serotonin and norepinephrine reuptake inhibitor; SPR, sepiapterin reductase; TRPV1, transient receptor potential cation channel subfamily V member 1; VGSC, voltage-gated sodium channel.

Clifford J. Woolf. Biological Psychiatry 2020; 87:74–81

Analgesic targets providing clinically validated efficacy

Target	Analgesic (Drug Function)	Discovery of Analgesic Activity, Year	Discovery of Target, Year
Mu Opioid Receptor	Morphine/opioids	1806	1973
COX-2	NSAIDs/COX-2 inhibitors (anti-inflammatory)	1899	1975
Sepiapterin Reductase	Sulfasalazine (anti-inflammatory)	1948	2011
Voltage-Gated Sodium Channel	Carbamazepine (antiepileptic)	1964	1982
NMDA Receptor	Ketamine (dissociative anesthetic)	1965	1983
Cav2.2	Ziconotide	1984	1984
Alpha2delta1	Calcium ion channel subunit gabapentin (antiepileptic)	1987	1997
$5\text{-HT}_{1B/D}$ Agonists	Triptans (migraine)	1988	1988
Serotonin-Norepinephrine Reuptake	Duloxetine (antidepressant)	1988	1988
CGRP	Erenumab (migraine)	2016	1988

Cav2.2, voltage-gated calcium channel 2.2; CGRP, calcitonin gene-related peptide; COX-2, cyclooxygenase 2; 5-HT, 5-hydroxytryptamine; NMDA, *N*-methyl-D-aspartate; NSAID, nonsteroidal anti-inflammatory drug.

Clifford J. Woolf. Biological Psychiatry 2020; 87:74–81

How were the targets discovered?

Route of Discovery	Successful Targets	Unsuccessful Targets
Following Clinical Discovery of Efficacy of Drug	MOR, COX-2, VGSC, SPR	
Following Preclinical Discovery of Efficacy of Drug	A2D, AT2R, KOR, 5HT1	FAAH1, CB2, CB1, Alpha2
Preclinical Discovery of Pain-Related Mechanisms	NMDAR, SNRI, Cav2.2, CGRP, NGF, Nav1.8, P2X, GABA	NK1, TRPV1, Kv7, p38, Cav3.2, P, CER2
Human Genetics		Nav1.7

5HT1, 5-hydroxytryptamine 1; A2D, alpha-2D–adrenergic receptor; Alpha2, alpha 2 receptor; AT2R, angiotensin II type 2 receptor; Cav, voltage-gated calcium channel; Cb, cannabinoid receptor; CCR2, C-C chemokine receptor type 2; CGRP, calcitonin gene-related peptide; COX-2, cyclooxygenase 2; FAAH1, fatty acid amide hydrolase 1; GABA, gamma-aminobutyric acid; KOR, kappa opioid receptor; Kv7, voltage-gated potassium channel 7; MOR, mu opioid receptor; Nav, voltage-gated sodium channel; NGF, nerve growth factor; NK1, neurokinin 1; NMDAR, *N*-methyl-D-aspartate receptor; P2X, purinergic receptor type 2x; p38, protein 38; SNRI, serotonin and norepinephrine reuptake inhibitor; SPR, sepiapterin reductase; TRPV1, transient receptor potential cation channel subfamily V member 1; VGSC, voltage-gated sodium channel.

Clifford J. Woolf. Biological Psychiatry 2020; 87:74–81

New targets in clinical development

Analgesic Target	Function of Target
NGF/TrkA	Reduce nerve growth factor or its action on its receptor
Nav1.8	Block sodium channel expressed by nociceptors
Biased Opioid Receptor GPCRs	Attempt to differentiate analgesic and adverse effects of mu opioid receptor activation
Kappa Opioid Receptor	Avoid the central dysphoria; peripheralized agonist
AT2R Angiotensin 2 Receptor	Contribute to immune activation of nociceptors; expressed in macrophages
mPGES1	Reduce prostanoid synthesis
P2X Purinergic Receptors	Block activation of nociceptors by ATP
GABA Subtype–Selective Modulators	Target GABA receptors in nociceptive circuits

AT2R, angiotensin II type 2 receptor; ATP, adenosine triphosphate; GABA, gamma-aminobutyric acid; GPCR, G protein–coupled receptor; mPGES1, microsomal prostaglandin E synthase 1; Nav1.8, voltage-gated sodium channel 1.8; NGF, nerve growth factor; P2X, purinergic receptor type 2X; TrkA, tropomyosin receptor kinase A.

Clifford J. Woolf. Biological Psychiatry 2020; 87:74–81

Analgesic target clinical failures

Target	Function of Target
NK1	Substance P/tachykinin receptor antagonist
TRPV1	Noxious heat/proton/capsaicin transducer antagonist
Nav1.7	Voltage-gated sodium channel blocker/nociceptor excitability
Cav3.2	Calcium channel blocker/synaptic transmission
Kv7	Potassium channel opener/nociceptor excitability
FAAH1	Enzyme inhibitor/cannabinoid enhancer
CB1/CB2	Cannabinoid receptors agonists
α2	Adrenergic receptor inhibitor
p38	Intracellular kinase inhibitor
CCR2	Chemokine antagonist

- α2, α2 adrenergic receptor
- Cav3.2, voltage-gated Ca++ channel 3.2
- CB, cannabinoid receptor
- CCR2, C-C chemokine receptor type 2
- FAAH1, fatty acid amide hydrolase 1
- Kv7, voltage-gated K+ channel 7
- Nav1.7, voltage-gated Na+ channel 1.7
- NK1, neurokinin 1
- p38, protein 38
- TRPV1, transient receptor potential cation channel subfamily V member 1

Clifford J. Woolf. Biological Psychiatry 2020; 87:74–81

Better management of analgesic treatment

Mitigation of drug-drug interactions

Metabolism of opioids

Opioid	Phase I Metabolism	Phase II Metabolism
Morphine	None	Glucuronidated by UGT2B7 (to morphine-3-glucuronide and morphine-6-glucuronide) and by UGT1A3
Codeine	10% *N*-demethylated by CYP3A4 (to norcodeine) 5% *O*-demethylated by CYP2D6 (to morphine)	80% glucuronidated by UGT2B7
Hydrocodone	*O*-demethylated by CYP2D6 (to hydromorphone) *N*-demethylated by CYP3A4 (to norhydrocodone)	CYP-metabolized products (e.g., hydromorphone) glucuronidated by UGTs
Oxycodone	*N*-demethylated by CYP3A4 (to noroxycodone) *O*-demethylated by CYP2D6 (to oxymorphone)	CYP-metabolized products (e.g., oxymorphone) glucuronidated by UGTs
Methadone	*N*-demethylated by CYP3A4, CYP2B6 Minor roles: CYP2C8, CYP2C19, CYP2D6, and CYP2C9	Glucuronidated by UGT2B7 and UGT1A3
Tramadol	*N*-demethylated by CYP3A4 and CYP2B6 *O*-demethylated by CYP2D6	None
Fentanyl	*N*-dealkylated by CYP3A4 (to norfentanyl)	None
Hydromorphone	None	Hepatic glucuronide conjugation by UGT2B7 and UGT1A3 (to hydromorphone-3-glucuronide)
Oxymorphone	None	Hepatic glucuronide conjugation by UGT2B7 and UGT1A3 (minor)
Tapentadol	None	Hepatic glucuronide conjugation by UGT2B7 and UGT1A9

Gudin J. Journal of Pain and Symptom Management http://dx.doi.org/10.1016/j.jpainsymman.2012.08.013

Number of clinically relevant interactions stratified by medication characteristics

Medication Characteristic	Total patients on protocol with characteristic	Clinically relevant[a] interactions with characteristic (%)
CYP450 metabolism	98	7 (7.1%)
P-glycoprotein transport	69	2 (2.9%)
QT prolongation	23	2 (8.7%)
pH dependent absorption	6	1 (16.7%)

[a]Clinical relevance was determined by study team review and defined as a drug-drug interaction that would require a medication change to ensure study medication safety/efficacy at enrollment

Marcath et al. BMC Cancer (2018) 18:1155

Categories for clinical effects of DDI

Severity level and examples of clinical effects per category

A: Clinically irrelevant effect

Increase or decrease in drug level without direct clinical consequences: tyrosine kinase inhibitors, endoxifen (active metabolite of tamoxifen)

B: Temporarily adverse effect

Decrease simvastatin/zolpidem level (by induction enzalutamide)

C: Longer-lasting adverse effect

Increase of everolimus level (by CYP3A4-inhibitors)

Increase of phenytoin plasma concentration (by capecitabine/5FU)

D: Long-lasting or permanent adverse effect

Increased toxicity capecitabine/5FU (by folic acid/metronidazole)

Decrease of plasma concentration of carbamazepine/phenytoin/valproic acid by certain anticancer agents

E: Severe adverse effect:

Increased toxicity mercaptopurine (by allopurinol/febuxostat)

Neuromuscular toxicity vinblastine/vincristine (by CYP3A4-inhibitors)

Hepatic veno-occlusive disease by busulfan (by itraconazole/ketoconazole)

F: Potentially fatal effect

Multi-organ failure (by combination of busulfan and metronidazole)

Death (by combination of methotrexate and trimethoprim or co-trimoxazole)

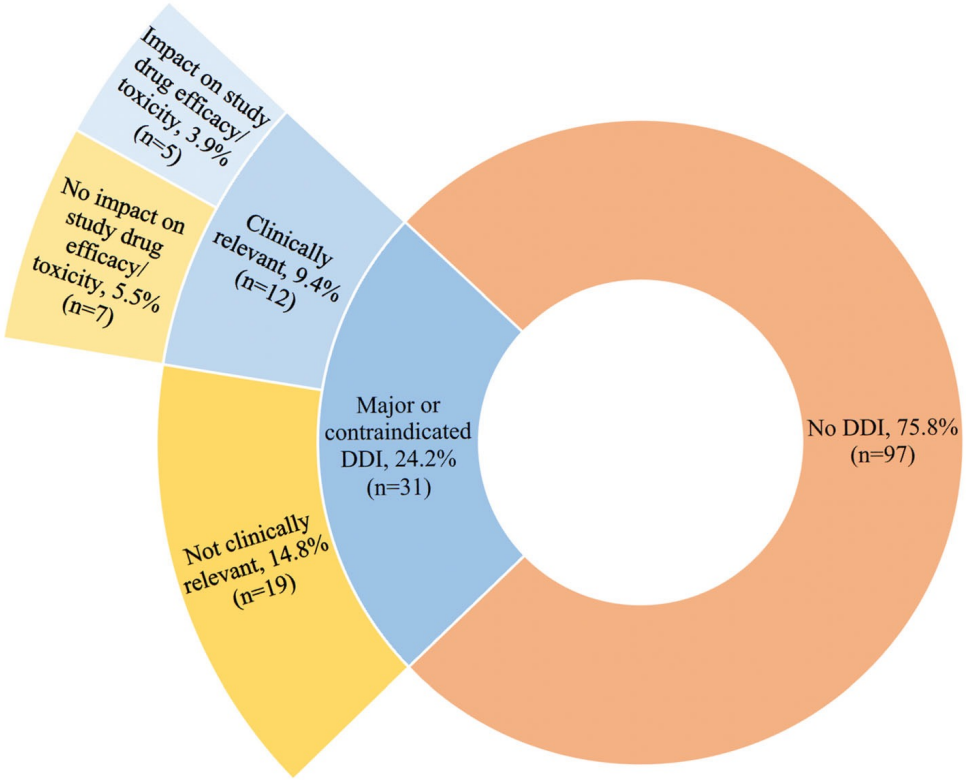
R.W.F. van Leeuwen, M. le Comte and A.K.L. Reyners et al. / Seminars in Oncology 49 (2022) 119–129

Categories for potential DDIs and advice for managing DDIs

Category	Advice
Drug-drug interaction (DDI) has been established, and the effect is clinically relevant.	Intervention is required, alert is generated
DDI has been established, but the effect is not clinically relevant	No intervention is required, no alert is generated
DDI has not been established	No intervention is required, no alert is generated

R.W.F. van Leeuwen, M. le Comte and A.K.L. Reyners et al. / Seminars in Oncology 49 (2022) 119–129

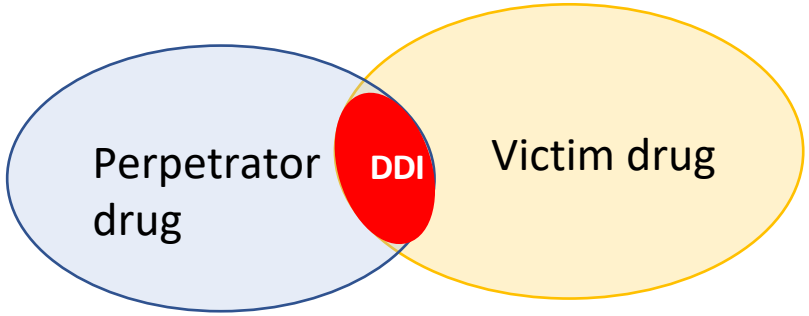
Drug-drug interactions in cancer patients and their clinical relevance



Marcath et al. BMC Cancer (2018) 18:1155

A bidimensional, oversimplified model is not predictive of clinically relevant DDI – Why?

A pharmacokinetic DDI model (the perpetrator is an inhibitor/inducer of victim drug metabolism; i.e., voriconazole and sunitinib)



A pharmacodynamic DDI model (drugs with overlapping AEs, i.e., clozapine and paclitaxel)

Danesi R et al., unpublished please do not reproduce

Because the following covariates are not taken into account while assessing the DDI

PK covariates

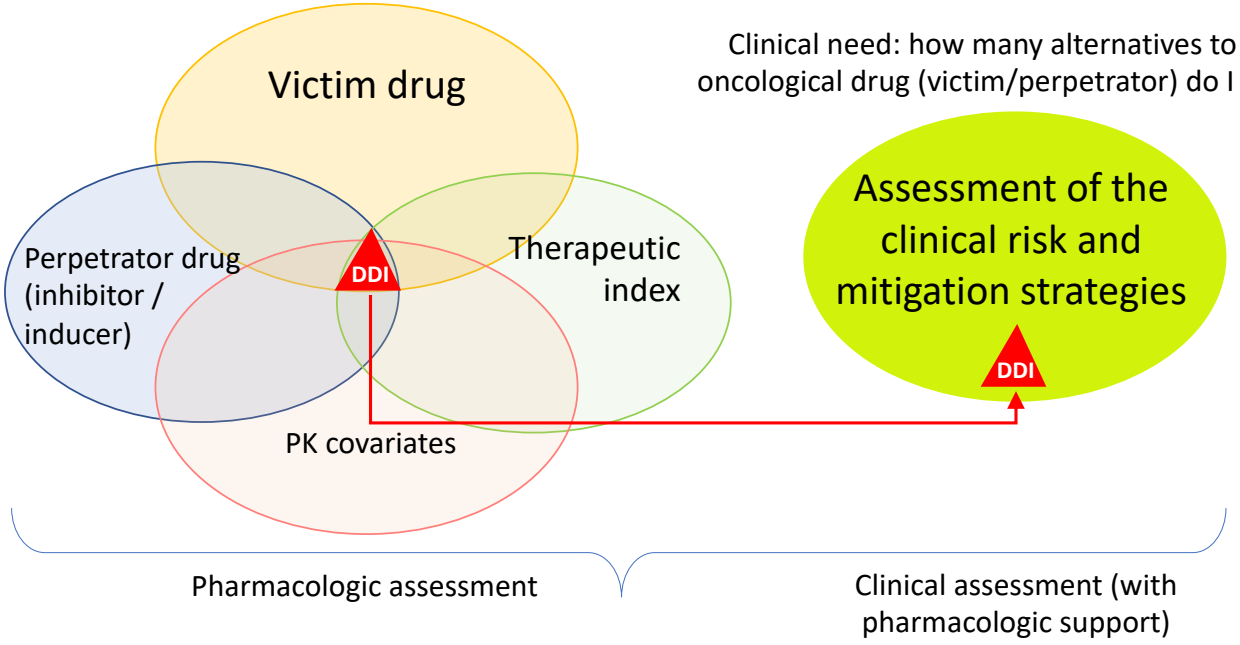
1. Weight, fat free mass
2. Liver/renal function
3. Age, Race, Gender
4. Clinical chemistry values
5. Hematologic values
6. Protein binding
7. Genotype of drug metabolising enzymes
8. Disease stage

Therapeutic index (TI)

1. It is the ratio between toxic vs. clinically effective drug concentrations.
2. A safe drug has a wide TI, while an oncology drug has a narrow TI

Joerger M. The AAPS Journal, Vol. 14, No. 1, March 2012
Tamargo J et al. Eur J Clin Pharmacol (2015) 71:549–567

Multiprofessional evaluation of DDI



DDI is associated to an increased risk/severity of already known (not unknown) ADRs

Danesi R et al., unpublished please do not reproduce

Better management of analgesic treatment

Improved diagnostics – It is time for pharmacogenetic testing to advance from an obscure unused test to a viable decision aid

Bringing pharmacogenetics to the bedside

When should ordering PGx testing be considered?

Prior to initiation of analgesic therapy.

(NCCN Category 2A Recommendation)

OR

During analgesic pharmacologic treatment when concerns of toxicity or lack of analgesic response are demonstrated or suspected.

(NCCN Category 2A Recommendation)

What PGx test should be ordered?

PREFERRED

Panel test including *CYP2D6*, *CYP2C9*, and *CYP2C19*.[1]

(Expert opinion)

OR

Single gene test(s) may be ordered based on the relevant therapy: opioids (*CYP2D6*), NSAIDs (*CYP2C9*), TCAs (*CYP2D6* and *CYP2C19*).[1]

(Expert Opinion)

D. Max Smith, William D. Figg. The Oncologist, 2023, 28, 189–192

Recommendations for PGx testing to guide pain management – CYP2D6

CYP2D6

Opioids: Codeine, Tramadol

UM: Avoid codeine and tramadol due to the risk of increased toxicity. Alternatives: another opioid (e.g., morphine, oxymorphone, hydromorphone) and/or nonopioid analgesics.

NM: Routine care.

IM: Routine care. If tramadol or codeine are ineffective then rotate to alternative therapy rather than dose modification.

PM: Avoid codeine and tramadol due to the risk of lack of analgesic effect. Alternatives: another opioid (e.g., morphine, oxymorphone, hydromorphone) and/or nonopioid analgesics.

D. Max Smith, William D. Figg. The Oncologist, 2023, 28, 189–192

FONDAZIONE 45 ANT FRANCO PANNUTI

Recommendations for PGx testing to guide pain management – CYP2C9

CYP2C9

NSAIDs: Celecoxib, Flurbiprofen, Ibuprofen, Meloxicam, Piroxicam

NM: Routine care.

IM[4]: Due to risk of toxicity, 1) avoid piroxicam and 2) avoid meloxicam or reduce dose by 50%.

PM: Due to risk of toxicity, 1) avoid piroxicam and meloxicam and 2) select alternatives (e.g., naproxen) or reduce dose to 25-50% for celecoxib, ibuprofen, and flurbiprofen.

D. Max Smith, William D. Figg. The Oncologist, 2023, 28, 189–192

FONDAZIONE 45 ANT FRANCO PANNUTI

Recommendations for PGx testing to guide pain management – CYP2C19 and CYP2D6

D. Max Smith, William D. Figg. The Oncologist, 2023, 28, 189–192

Conclusions

- The high efficacy of opioids, which have associated risks of addiction, tolerance, and dependence, has been a major driver of the opioid crisis, together with the availability, overprescription, and diversion of these drugs.
- Eliminating opioids without an effective replacement is, however, no solution, as it substitutes one major problem with another.
- For these reasons, we need to discover novel analgesics whose mechanisms do not involve the mu opioid receptor but that have high analgesic potency and low risk of adverse effects.
- This perspective, together with the adoption of improved management strategies (PGx implementation, DDI mitigation), will make pain treatment more effective than before.