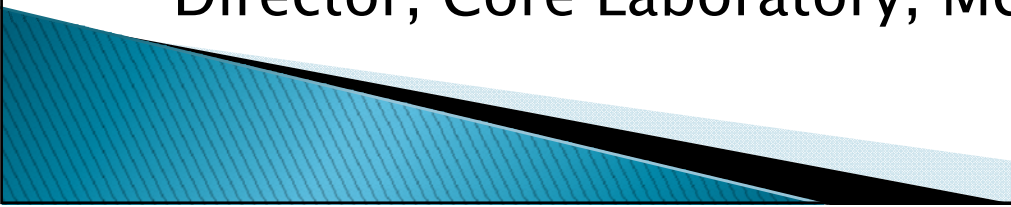
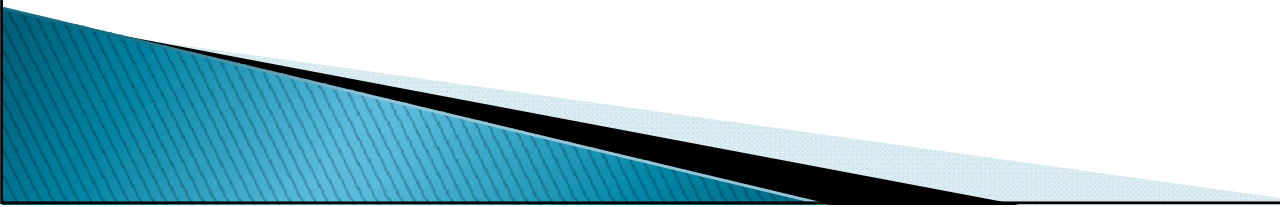


Laboratory Support of Pain Management: Beyond Urine Drug Testing

Catherine Hammett–Stabler, PhD, DABCC, FACB
Department of Pathology and Laboratory Medicine
Director, Core Laboratory, McLendon Clinical Laboratories



Outline

- ▶ Pain and the pain clinics
 - ▶ Opiates, opioids, and the risk of misuse
 - ▶ Testing
 - ▶ Where should we go?
- 

The Complexity of Pain

Whatever the experiencing person says it is, existing whenever s/he says it does

McCaffrey, 1968

An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

International Association for the Study of Pain, 1979

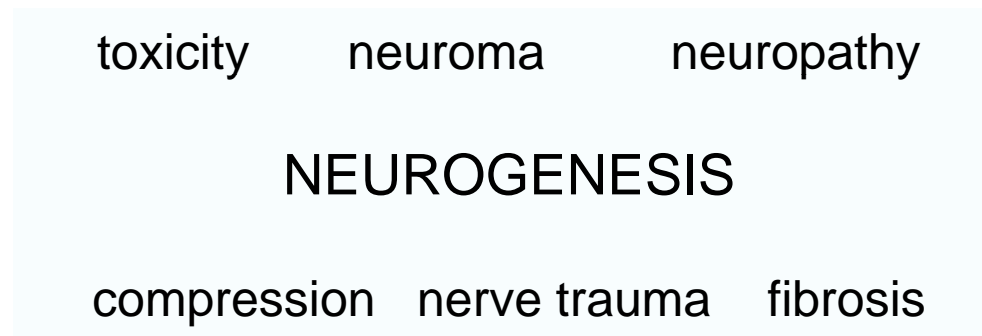


Mechanisms of Pain

- ▶ Pathophysiology
 - Nociceptive
 - Neuropathic
- ▶ De novo
- ▶ Sensitization

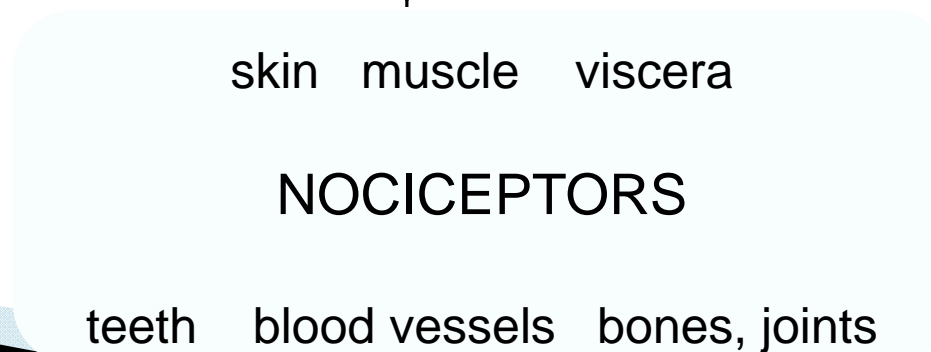
INFLAMMATION

sensitization



PERIPHERAL NERVE

Spinal Cord
Dorsal Horn



Pain in USA

- Most common reason for seeking medical care
- ▶ Acute pain: 25 million
 - Complex unpleasant experience with emotional, cognitive, and sensory, features
 - Occurs in response to tissue trauma
 - Mechanisms defined
 - Resolves on healing
 - Biologically useful
- ▶ 90% of cases are treatable
- ▶ Chronic: 50 million
 - Pain extending beyond the period of healing with low levels of identified pathology
 - Caused by pathology or de novo
 - Complex, unclear mechanisms
 - Psychological and environmental components
 - Persists
 - Disrupting to daily functions

The Joint Commission, 2005

Pain in USA

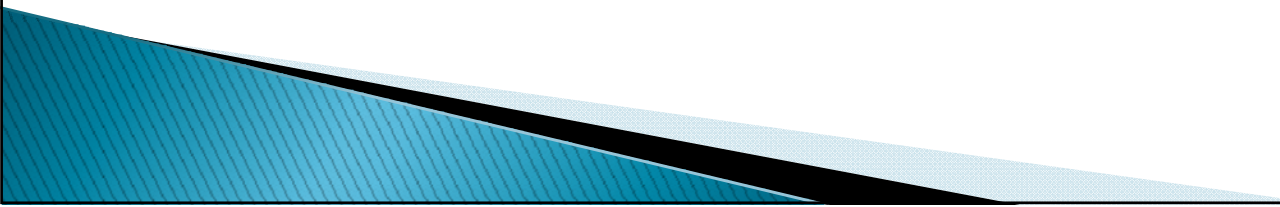
- Most common reason for seeking medical care
 - ▶ \$100 billion (US)
 - ▶ Chronic pain patients use health care services (in-patient and out-patient) 5x non-pain patients
 - ▶ Increased length of stay
 - ▶ Poorer outcome
 - ▶ >50 million work days lost

Treatment

- ▶ Physical Therapies
 - Electrical stimulation
 - Physical therapy
 - Surgery
 - Acupuncture
- ▶ Psychological counseling and behavior modification

- ▶ Pharmacotherapy
 - Analgesics and anti-inflammatory drugs
 - Opiates and opioids
 - Anesthetics
 - Antidepressants
 - Antiepileptics

Therapeutic Agents

- ▶ Opiates, opioids, mixed agonists–antagonists
 - ▶ Benzodiazepines
 - ▶ Antidepressants
 - ▶ Antiinflammatories
 - ▶ Antiepileptics
- 

Opiates and Opioids

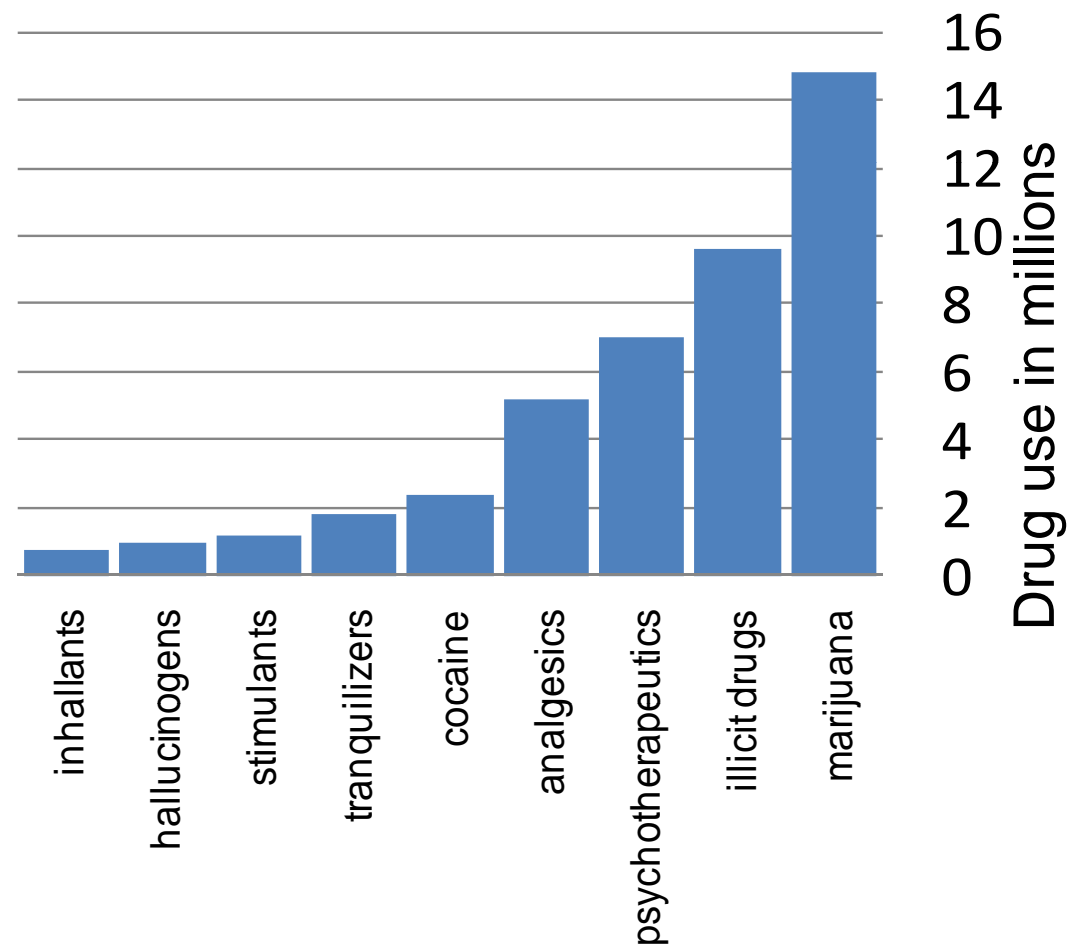
- ▶ Narrow therapeutic index



- ▶ Large interpatient variability
 - >40-fold dosage variation for morphine post-operatively in hip replacement patients
- ▶ High potential for abuse

Drug Abuse or Misuse

- 6-15% of general population admits to using or experimenting with illicit drugs
- 8.3% or 20.4 million admit to current use
 - 7 million misuse prescriptive drugs
 - 5.2 million misused analgesics



2008 National Survey on Drug Use and Health

Identifying Drug Seeking Behavior and Illicit Drug Use Among Pain Patients

- ▶ Detection of problem patients based on behaviors
 - Healthcare providers detected “bogus” patients 10% of time
 - 14% correctly predicted based on “gut instinct”
 - 46–48% correctly predicted based on patient surveys
 - ~9% of patients correctly self-report

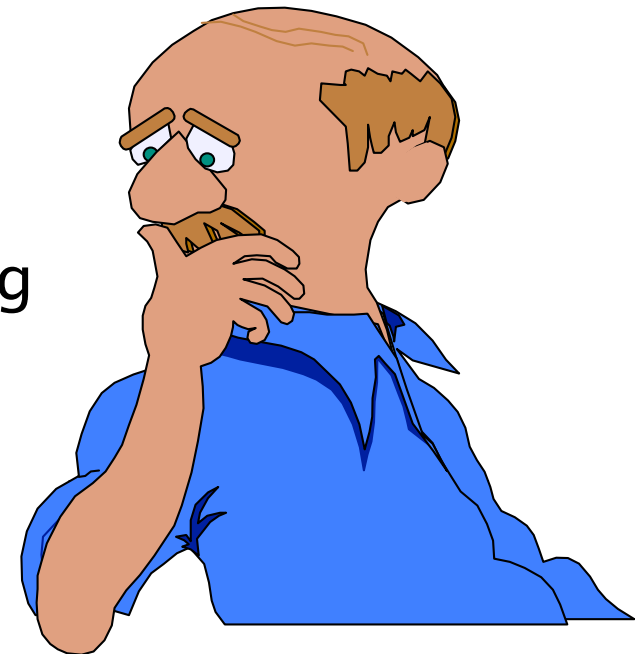
Clin J Pain 2007;23:173-9
Pain Physician 2004;7:431-7

Detection and Deterrent Techniques

- ▶ Contracts
- ▶ Self-reports
- ▶ External data
 - Biological testing
 - Spouses or others

Urine Drug Testing

- ▶ Initially designed for Work Place Drug Testing
- ▶ Random Urine
 - Readily available
 - Non-invasive collection
 - Drug and/or drug metabolite concentrated
 - Aqueous media – easily prepared for testing
- ▶ Adopted by clinical labs
 - Economic and technical reasons
 - Broader spectrum of use
 - From assessment of mental status alteration to clinical trials

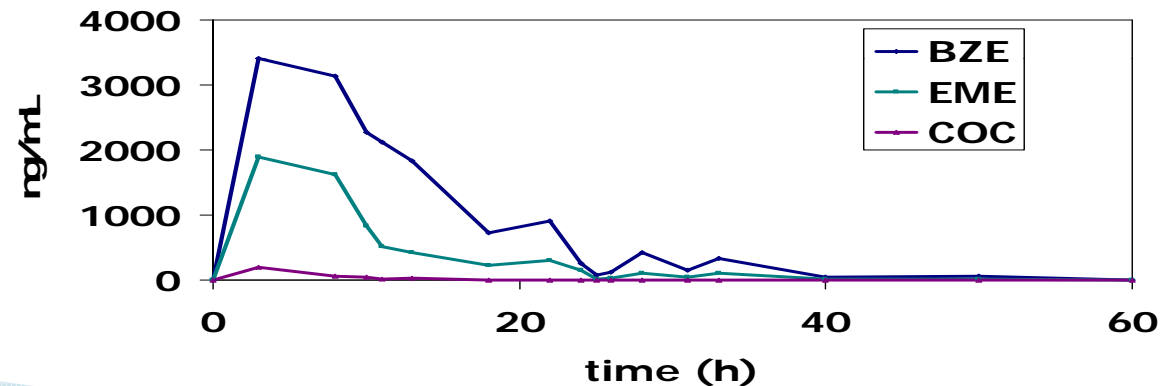


Random urines:

the bane of chemistry testing

- Limitations
 - Represent a single point in time
 - Do not relate to patient's current presentation
 - Compounds detected are metabolic by-products
- Excretion rate
 - Renal function
 - Urine pH and volume
 - Hydration state

Excretion Pattern of Cocaine and metabolites



Collection and Trust

- ▶ In the clinical setting, trust is important to the relationship!
- ▶ Substituted urine or another yellow liquid
- ▶ Common 'added' adulterants:
 - H₂O; Detergents, bleach, salt, ammonia, acids
 - Glutaraldehyde
 - Nitrites
 - Chromates
 - Peroxide and peroxidase
- ▶ Common ingested adulterants:
 - H₂O, numerous products, many myths
 - Some products contain creatine and vitamin B



Testing

- Two tiers of testing are used
 - ▶ Immunoassays for screening
 - Antibody based tests
 - Analyte originally selected to give “*good window of detection*”
 - ▶ Specificity of antibodies (cross-reactivity) varies
 - ▶ Sensitivity (cut-off)
 - ▶ Confirmation testing using a second analytical procedure with higher specificity (narrow list of compounds detected or identified)
 - Does not look for every drug or chemical in class
 - ▶ And with better sensitivity
 - Cut-offs are lower
 - but still NOT 0!
 - ▶ Gas chromatography/mass spectrometry (GC/MS)
 - ▶ Liquid chromatography/tandem mass spectrometry (LCMSMS, UPLCMS)

Can Urine Drug Testing identify and reduce abuse?



Pain Clinic Studies of UDT

Study	subjects	Problem UDS (%)	Findings
Hariharan et al. JIGM 22:485;2007	330	53 (38%)	illicit substances (Cocaine, THC) No confirmations Did not consider opiates
Michna et al. Clin J Pain 23:173;2007	470	210 (44.8%)	20.2% illicit substances 14.5 % non-prescribed opioid 10.2 % missing opioid
Ives et al. BMC Health Serv Res 6:46;2006	196	62 (32%)	38.7% cocaine 1.6% amphetamine 24.2 % missing opioid 14.5 % non-prescribed opioid
Manchikanti, et al Pain Physician 9:123;2006	500	80 (16%)	54% THC 5% cocaine 2% amphetamine
Katz et al. Clin J Pain 18:S76;2002	122	36 (29%)	16% cocaine 55.5% THC 22.2% non-prescribed opioid
Fishbain et al. Clin J Pain 15:184;1999	226	105 (46.5%)	6.2% THC 2.2% cocaine 8.8% incorrect opioid

Ives, et al. UNC IM Pain Clinic

- ▶ 199 consecutive patients referred from UNC IM
 - Non-cancer pain > 3 m duration, receiving opioids
 - Difficult management, suspected misuse
 - Monitored monthly during medication titration phase, then quarterly
 - Anti-inflammatory agents, analgesics, long-acting or sustained-release opioids
 - 196 enrolled/ 7 lost by end of year
- ▶ Mean age 52 y
- ▶ 55% Male
- ▶ 75% Caucasian
- ▶ Socioeconomic demographics
 - 85% income <\$20k
 - Education
 - 60% high school degree
 - 54% <9th g reading level
 - Insurance
 - 62% Medicaid or Medicare
 - 30% Uninsured
- ▶ Functionality
 - 57% Disabled
 - 74% Depressed
- ▶ History of drug abuse
 - 28% ETOH and 28% cocaine
- ▶ Legal issues
 - 12% drug conviction
 - 11% DUI

UNC IM Pain Clinic

- ▶ Contract: agreed to
 - Receive O/CS from UNC IM PC only
 - Use 1 pharmacy
 - Not share or sell meds
 - Not abuse ETOH
 - Not use cocaine, amphetamines (counseled to avoid THC, monitored)
 - Submit to background checks
 - Renewals or refills only during regular hours, not by telephone
 - Consideration for replacing lost, stolen meds only during clinic visit
 - **Submit to UDT**
 - **Creatinine + screen; confirmation of positive opiates, unexpected results or when concerned**

UNC IM Pain Clinic

- ▶ Misuse defined as
 - Negative UDT x2 for prescribed o/cs
 - Inconsistent UDT
 - Stimulant positive (cocaine, amphetamine)
 - Evidence of doctor collecting
 - Drug diversion
 - Prescription forgery
- ▶ Misuse monitoring
 - Clinical history and external records
 - Medication(s) review
 - Communication with pharmacies and providers
 - UDT

Detected Misuse

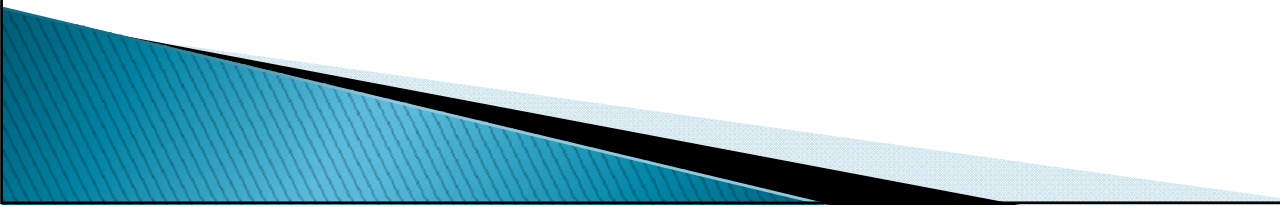
- ▶ Problem Results 32%
 - Illicit drugs
 - Amphetamines 1.6%
 - Cocaine 38.7%
 - THC 18%
 - Inconsistent urines 14.5%
 - Missing opioid (negative) 24.2%
- ▶ Doctor collecting 16%
- ▶ Prescription forgery 3.2%
- ▶ Diversion 1.6%

Predictors of Misuse

	Non-misuse (%)	Misuse (%)	Relative risk
Male gender	38	59.7	1.56
Multiple drug convictions	1	11	15.13
Drug or DUI conviction	11	40	3.60
Hx cocaine	21	68	3.30
(+) THC	12	33	2.70

Opportunities

- ▶ Education
 - ▶ Where should we go?

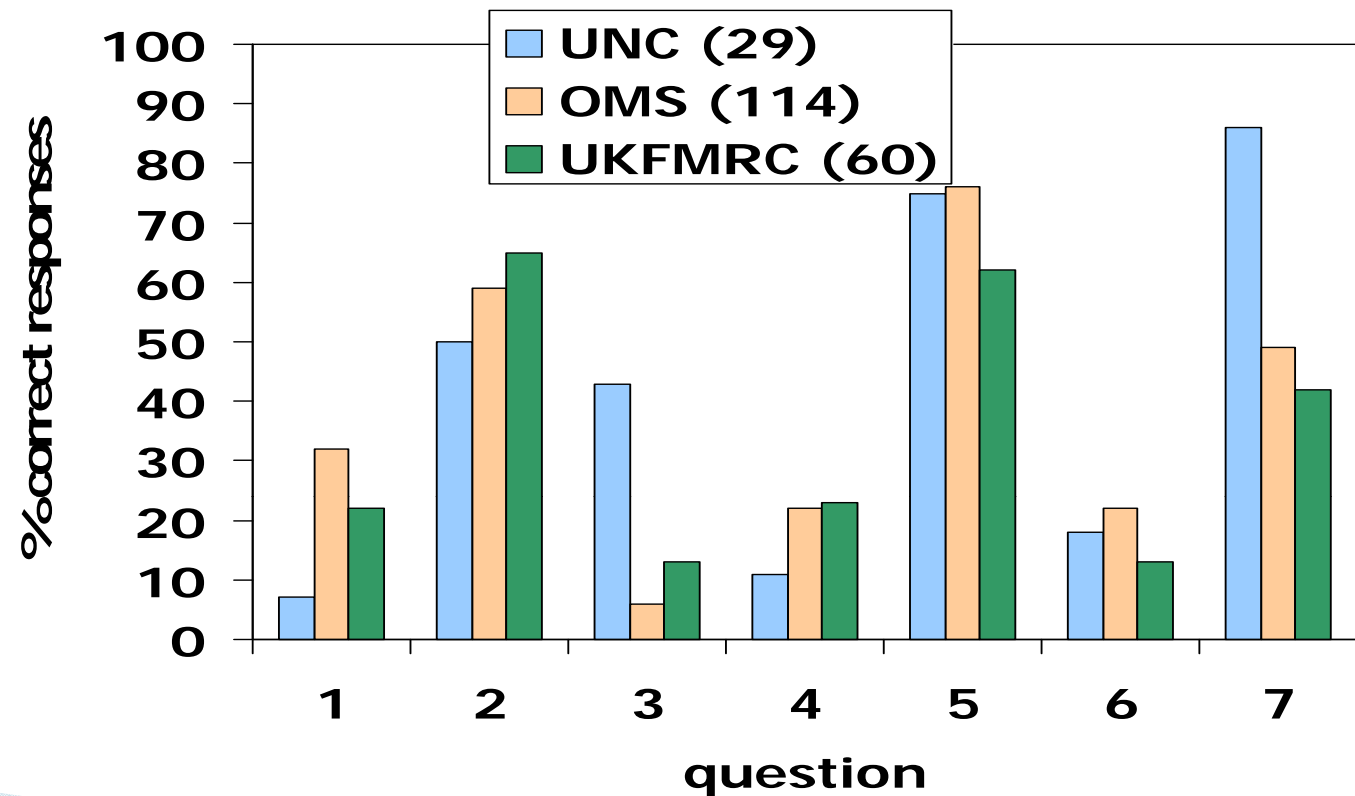
 - ▶ Testing
 - ▶ Personalized medicine
- 

Education and consultative services

- Durback et al *Vet Hum Toxicol* 1998
 - 81 ED physicians
 - 5% correctly identified drugs detected by their lab's UDS,
 - 73% thought UDS detected all benzodiazepines
- Reisfield, Webb, Bertholf, et al *J Opioid Manag* 2007
 - Opioid Management Society and KY Family Medicine Review Course
 - 231 physicians, 174 returned surveys
 - 123 pain mgt and 51 not involved in pain mgt
 - OMS: 19% boarded in pain mgt, 6% addiction med or psychiatry
- UNC (not published)
 - Family Medicine, Psychiatry, Anesthesiology
 - 41 distributed, 29 returned surveys

Comparison of Correct Responses by Question

1. Tylenol #3
2. MS Contin
3. Heroin
4. Oxycontin + poppy seeds
5. Passive inhalation of THC
6. Negative opiate screen
7. Negative screen for any drug



Important Points

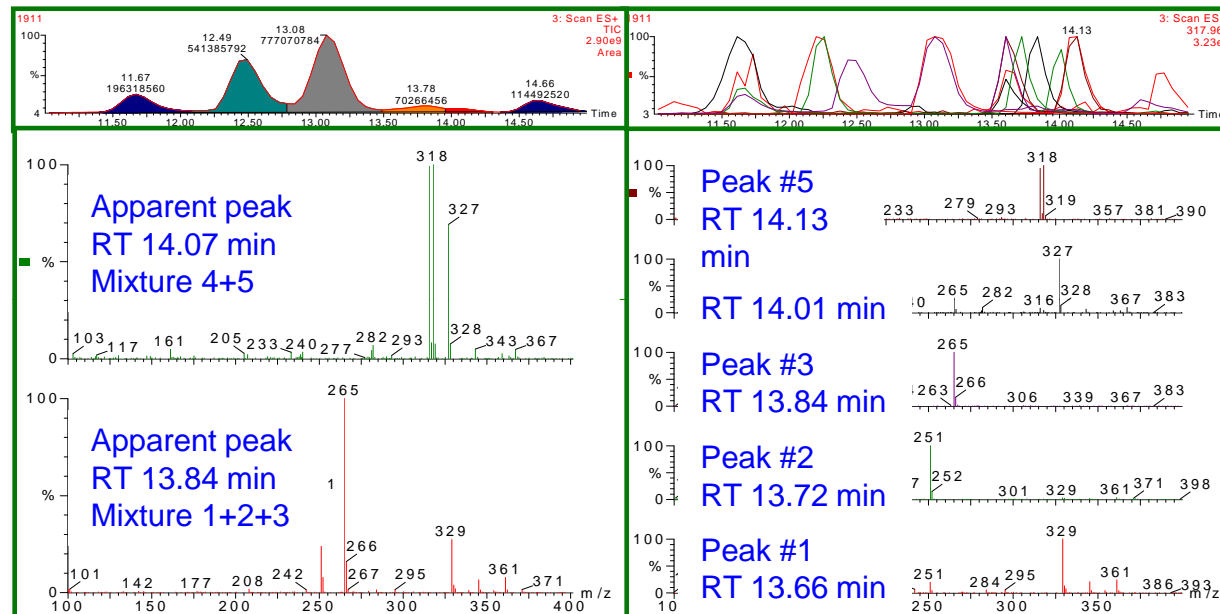
- ▶ Physician knowledge of UDT interpretation is inadequate
 - 75% correctly answered less than 50% of questions
 - Questions requiring pharmacology knowledge missed most often
 - OMS demonstrated that many who use UDT routinely are not more proficient in interpretation
- ▶ UKFM: < 25% of physicians indicated they consult the laboratory director about results

Testing: Cross-reactivity Studies

Sample	µg/mL	AMP	Barb	Benz	COC	METH	OPI	PCP	PPX	THC
Immunoassay 1										
DFU	0	26	8	0	60	0	24	118	33	82
Tramadol	1250	397	24	0	0	2023	584	1705	163	123
o-DMT	1000	22	5	0	0	1413	23	343	22	1653
n-DMT	100	29	10	0	0	367	15	99	28	1634
Immunoassay 2 and 3										
Tramadol	1250	0	0	0	0	0	0	0	0	0
Sertraline	1000	0	0	410	0	305	377	-	360	0
DMS	500	158	0	221	0	70	0	-	268	0
Bupropion	16000	230	0	0	0	0	0	-	0	0
OH-B	16000	333	0	0	0	0	0	-	0	0
Buspirone	8000	0	0	0	0	0	0	-	0	0
Buprenorphine	16000	0	0	0	0	0	0	-	0	0

Testing: Back to the Future

- ▶ Return to chromatography based testing and broader screens with higher specificity
- ▶ LC or UPLC MS/MS
- ▶ Discovery
 - minor metabolic pathways
 - pharmaceutical contaminants



Testing

- ▶ Should we consider pain TDM?
- ▶ When should pharmacogenetics be used?
- ▶ Cases
 - 42 yo female, fentanyl
 - Reports inadequate control by d3
 - 48 yo female, oxycodone/oxycontin
 - Adequate control but low urine concentrations

Genetics of Analgesia Vs Genetics of Pain

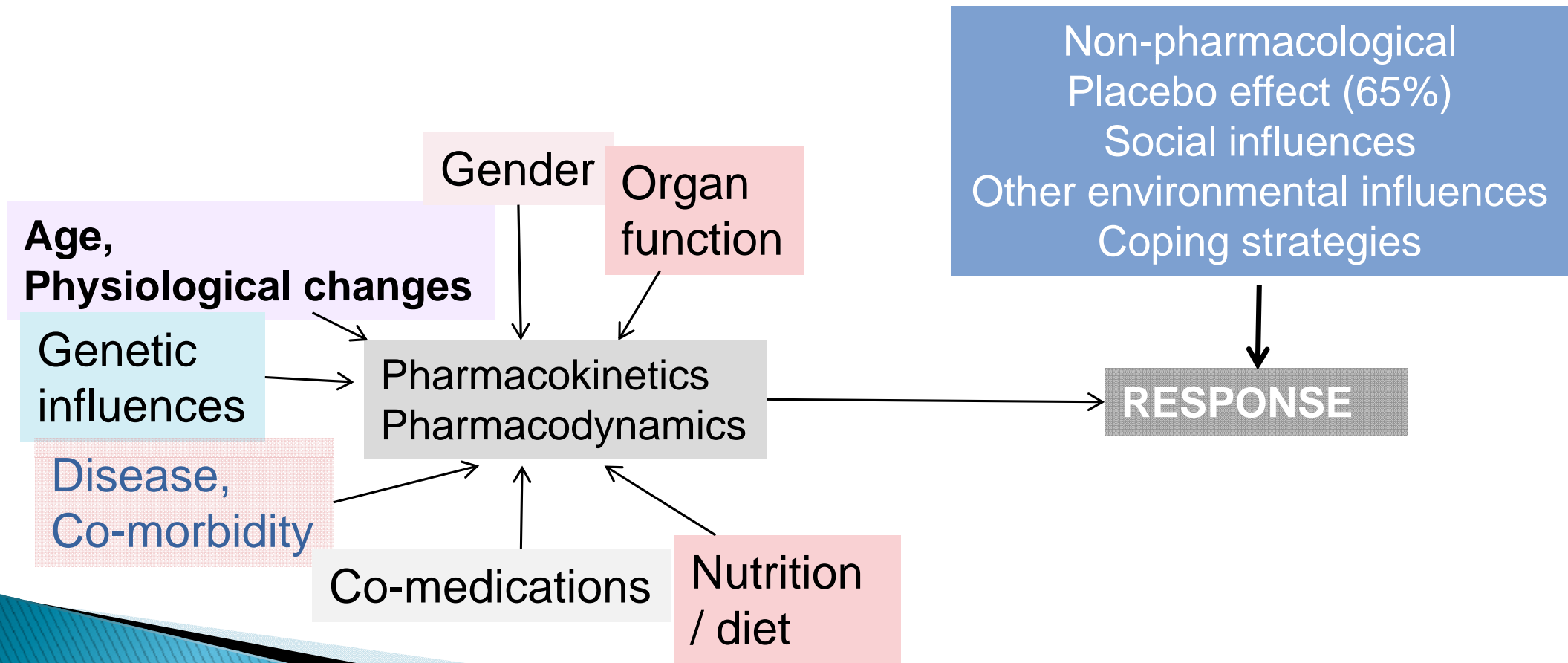
Drug metabolism

- ▶ CYP3A4, CYP3A5
- ▶ CYP2D6
- ▶ CYP2B6
- ▶ CYP2C19
- ▶ UDP-glucuronosyltransferases (UGTs)
- ▶ Glutathione-S-transferases
- ▶ N-acetyltransferases

Experience and Therapeutic response

- ▶ μ -opioid receptor (OPRM1)
- ▶ δ -opioid receptor
- ▶ Catechol-*O*-methyltransferase (COMT)
- ▶ Voltage-gated sodium channel Na(v)1.7
- ▶ HSAN-I, II, III, IV, V
- ▶ Melanocortin-1 receptor (MC1R)
- ▶ Vanilloid receptor
- ▶ Guanosine triphosphate cyclohydrolase (GCH1)
- ▶ Arachidonic acid pathways
- ▶ ATP-binding Cassette transporters
 - P-glycoprotein
- ▶ Solute carrier influx transporters
- ▶ β -Arrestin 2
- ▶ Nerve growth factors

Variables Contributing to Analgesic Response



Promising but Complicated

- ▶ Response to drugs is rarely determined by a single gene polymorphism, but rather by heterogeneity in multiple genes affecting drug metabolism, transportation, and effector protein/receptor.

Stamer and Stuber. Expert Opin Pharmacother 2007;8:2235

Acknowledgements

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