Analgesic Impact On Physical Function In Older Veterans With Arthritis

HSR&D Cyberseminar

Spotlight on Pain Management (SoPM)

December 4, 2018

Ula Hwang, MD, MPH

James J. Peters VAMC, GRECC

Acknowledgements

- Funding
  - VA HSR&D Merit (IIR 12-106 Hwang)
- EAASE Site Investigators
  - Matthew Bair, MD MS
  - Cynthia Brandt, MD MPH
  - Robert Kerns, PhD
  - Erin Krebs, MD MPH

Objective

- Trends in analgesic prescribing and concerns about analgesic safety impacting outpatient pain treatment.
- Changes in prescribing may disproportionately impact aging veteran population.

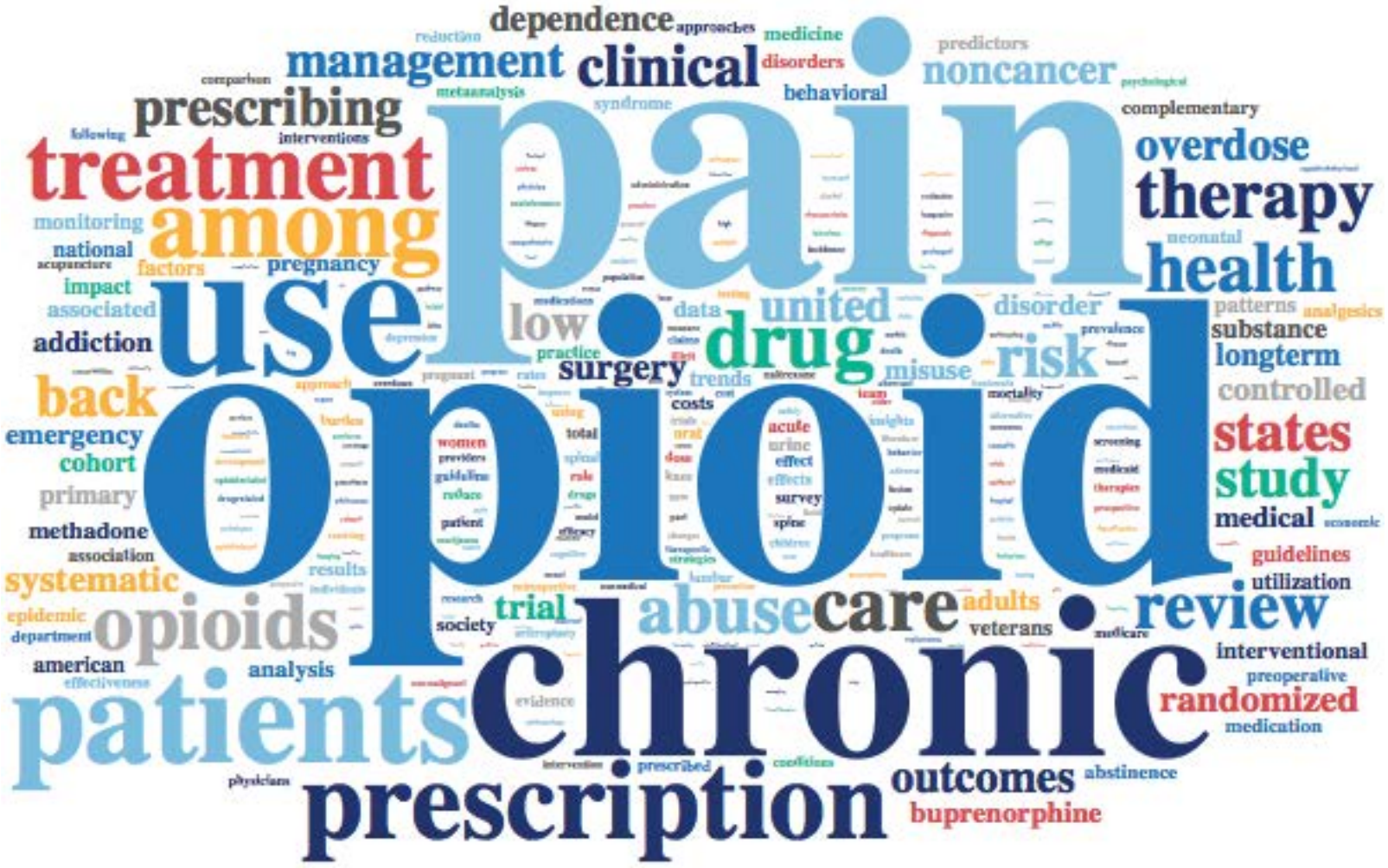
Objective:

To inform participants about the comparative effectiveness of different analgesic types on pain and function in older Veterans.

Today's Session

1. Overview of analgesic prescribing and older veterans
2. Recent & Relevant Studies with Arthritis Analgesics
3. Our study: EAASE
4. OA hip/knee Pain, Stiffness, Function outcome
5. Early results
6. Questions & Comments

OVERVIEW


dependence
approaches
medicine
predictors
management
clinical
disorders
noncancer
comparison
metaanalysis
behavioral
prescribing
syndrome
complementary
following
interventions
pain
overdose
treatment
therapy
monitoring
among
neonatal
national
factors
pregnancy
health
impact
use
low
data
united
disorder
patterns
analgesics
associated
drug
substance
addiction
practice
risk
longterm
surgery
trends
misuse
back
opioid
controlled
costs
mortality
emergency
states
cohort
study
primary
medical
methadone
guidelines
association
results
utilization
systematic
abuse
care
adults
review
epidemic
opioids
trial
society
veterans
department
interventional
american
analysis
preoperative
effectiveness
randomized
patients
chronic
evidence
medication
prescribed
outcomes
abstinence
physicians
prescription
buprenorphine

Background

- Opioid prescriptions doubled in last decade, advent of opioid crisis in last several years.
- Focus on chronic pain management and related therapies.
- Less on analgesic safety and effectiveness when initiated.
- OA prevalence increases with age.
- Older adults with OA experience pain that affects their physical function ← *ideal to study.*

Background

- 1 in 4 US adults with doctor-diagnosed arthritis.
- 1 in 3 Veterans with Arthritis. (Murphy, MMWR, 2014)
- In US, lifetime risk of osteoarthritis (OA):
  - Knee OA 45%
  - Hip OA 25% (Murphy, MMWR, 2008)
- Opportunity to study analgesics, such as NSAIDs and Opioids.
- Often measured by their capacity to reduce pain, while improvement in physical function has been overlooked.

RECENT & RELEVANT STUDIES

Recent Studies

- Few studies evaluating comparative safety of analgesics and serious adverse drug events – many are meta-analyses or descriptives of national datasets.
- 65% of US patients with OA are prescribed NSAIDs.
  (Gare et al, Pain Pract, 2012)
- National Injury Surveillance Adverse Drug Event (ADE) data: 3 drug classes (anticoagulants, diabetes agents, and **opioid analgesic**) implicated in 60% of ED ADE visits for older adults.
  (Shehab et al, JAMA, 2016)

Recent Studies

- Pragmatic 12-month trial, 240 subjects randomized to opioid and non-opioid therapy.
- Veterans with moderate to severe **chronic** hip/knee OA or back pain, **despite non-opioid analgesic use**.
- ***No differences in pain-related function*** with long term opioid vs. non-opioid use.
- Medication-related symptoms increased.
- No difference in hospitalizations, ED visits, falls.
  (Krebs et al., JAMA, 2018)

Analgesics in Nonmalignant pain and Arthritis – initiation of analgesics

ORIGINAL INVESTIGATION

The Comparative Safety of Opioids for Nonmalignant Pain in Older Adults

Daniel H. Solomon, MD, MPH; Jeremy A. Rassen, ScD; Robert J. Glynn, PhD, ScD; Katie Garneau, BA; Raisa Levin, MSc; Joy Lee, BA; Sebastian Schneeweiss, MD, ScD

Background: Severe nonmalignant pain affects a large proportion of adults. Optimal treatment is not clear, and opioids are an important option for analgesia. However, there is relatively little information about the comparative safety of opioids. Therefore, we sought to compare the safety of opioids commonly used for nonmalignant pain.

Methods: We devised a propensity-matched cohort analysis that used health care utilization data collected from January 1, 1996, through December 31, 2005. Study participants were Medicare beneficiaries from 2 US states who were new initiators of opioid therapy for nonmalignant pain, including codeine phosphate, hydrocodone bitartrate, oxycodone hydrochloride, propoxyphene hydrochloride, and tramadol hydrochloride; none had a cancer diagnosis, and none were using hospice or nursing home care. Our main outcome measures were incidence rates and rate ratios (RRs) with 95% confidence intervals (CIs) for cardiovascular events, fractures, gastrointestinal events, and several composite end points.

Results: We matched 6275 s
oid groups. The groups were
characteristics. The risk of car
lar across opioid groups 30 d
therapy, but it was elevated
CI, 1.27-2.06) after 180 da
codone, after 30 days of opio
ture was significantly reduced
CI, 0.16-0.28) and propoxyp
ers. The risk of gastrointestin
fer across opioid groups. A
evated after 30 days for oxy
1.47-4.00) and codeine (2.
pared with hydrocodone use

Conclusions: The rates of
adults using opioids for non
cantly by agent. Causal infer
designs, but these results sh
further study.

Arch Intern Med. 2010;170(22

ORIGINAL INVESTIGATION

The Comparative Safety of Analgesics in Older Adults With Arthritis

Daniel H. Solomon, MD, MPH; Jeremy A. Rassen, ScD; Robert J. Glynn, PhD; Joy Lee, BA; Raisa Levin, MS; Sebastian Schneeweiss, MD, ScD

Background: The safety of alternative analgesics is unclear. We examined the comparative safety of nonselective NSAIDs (nsNSAIDs), selective cyclooxygenase 2 inhibitors (coxibs), and opioids.

Methods: Medicare beneficiaries from Pennsylvania and New Jersey who initiated therapy with an nsNSAID, a coxib, or an opioid from January 1, 1999, through December 31, 2005, were matched on propensity scores. We studied the risk of adverse events related to analgesics using incidence rates and adjusted hazard ratios (HRs) from Cox proportional hazards regression.

Results: The mean age of participants was 80.0 years, and almost 85% were female. After propensity score matching, the 3 analgesic cohorts were well balanced on baseline covariates. Compared with nsNSAIDs, coxibs (HR, 1.28; 95% confidence interval [CI], 1.01-1.62) and opioids (1.77; 1.39-2.24) exhibited elevated relative risk for cardiovascular events. Gastrointestinal tract bleeding risk was reduced for coxib users (HR, 0.60; 95% CI, 0.35-1.00) but was similar for opioid users. Use of coxibs and nsNSAIDs resulted in a similar risk for fracture; however, fracture risk was elevated with opioid use (HR, 4.47; 95% CI, 3.12-6.41). Use of opioids (HR, 1.68; 95% CI, 1.37-2.07) but not coxibs was associated with an increased risk for safety events requiring hospitalization compared with use of nsNSAIDs. In addition, use of opioids (HR, 1.87; 95 CI, 1.39-2.53) but not coxibs raised the risk of all-cause mortality compared with use of nsNSAIDs.

Conclusions: The comparative safety of analgesics varies depending on the safety event studied. Opioid use exhibits an increased relative risk of many safety events compared with nsNSAIDs.

Arch Intern Med. 2010;170(22):1068-1078

Analgesics in Arthritis

- Solomon, et. al. “The Comparative Safety of Analgesics in Older Adults with Arthritis.” Arch Intern Med 2010.
  - Medicare pharmacy claims for beneficiaries in PA and NJ 1999-2005. No cancer, hospice, or concurrent analgesics.
  - Initial analgesic exposure: nsNSAIDs, coxibs, opioids
  - Propensity score matched comparisons.
  - “Opioid use with increased relative risk of many safety events.” (cardiovascular (MI), fracture, events requiring hospital, and all cause mortality)

Analgesics in Arthritis

- Multiple commentaries and editorials during subsequent year challenging findings of cardiovascular risk with opioids.
- Many commentaries about study limitations:
  - Over-the-counter (OTC) analgesic drugs
  - Inpatient exposure to analgesics
  - Adjusting for confounding patient risk factors (i.e., smokers and opioids)

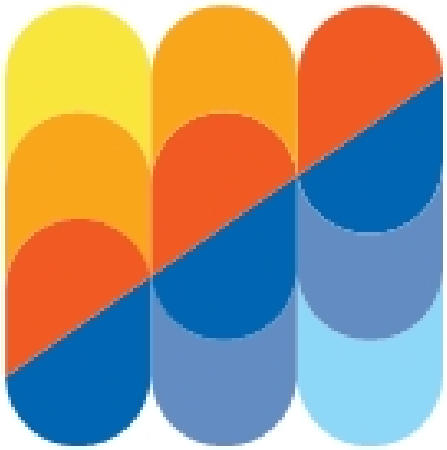
(Becker et al., Arch Intern Med, 2010)

(Devitt, Arch Intern Med, 2011)

(Rasteger, Arch Intern Med, 2011)

→ OPPORTUNITY to LEVERAGE VHA data…

EVALUATING
ARTHRITIS
ANALGESIC
SAFETY &
EFFECTIVENESS



EAASE

Veterans Health Administration

EAASE Design

- Project 1: Prospective, multicenter (4 VAs), longitudinal telephone survey administered at baseline, 30D, 90D, and 180D.
- ~100 question survey [no compensation for participation]
- April 2015 to July 2018.
- [Project 2: Leveraging retrospective data from VHA national integrated health care system]
- [questions about concurrent analgesic use, OTC, other therapies, beliefs about analgesics, substance use, healthcare utilization, etc.]

EAASE Design

- Project 1: Prospective, multicenter (4 VAs), longitudinal telephone survey administered at baseline, 30D, 90D, and 180D.
- ~100 question survey [no compensation for participation]
- April 2015 to July 2018.
- [Project 2: Leveraging retrospective data from VHA national integrated health care system]
- [questions about concurrent analgesic use, OTC, other therapies, beliefs about analgesics, substance use, healthcare utilization, etc.]

EAASE Design

- Current presentation **Baseline Survey** and **30-day Follow-up Survey** results:
  - Baseline survey administered within 30 days of receiving an analgesic prescription.
  - 30-day (30D) survey within 30 days of baseline.

Participants

- Age ≥ 50
- Had ICD-9/10 diagnoses of hip or knee OA and did not deny hip/knee arthritis during baseline survey
- ***Analgesic-free during 180+ days prior to this index analgesic prescription***
- Prescribed an outpatient analgesic medication:
  - *Opioid vs.*
  - *NSAID vs.*
  - ***Control medication*** (any *non*-analgesic prescription)
- No diagnosis of cancer or on hospice

Analgesic Categories

Opioids	NSAIDs
Acetaminophen-Codeine	Diclofenac
Acetaminophen-Hydrocodone	Etodolac
Acetaminophen-Oxycodone	Ibuprophe
Codeine	Indomethacin
Fentanyl	Ketoprofen
Hydromorphone	Ketorolac Tromethamine
Methadone	Meloxicam
Morphine	Naproxen
Oxycodone	Piroxicam
Tramadol	Salsalate
Hydrocodone	Sulindac
	Tolmetin

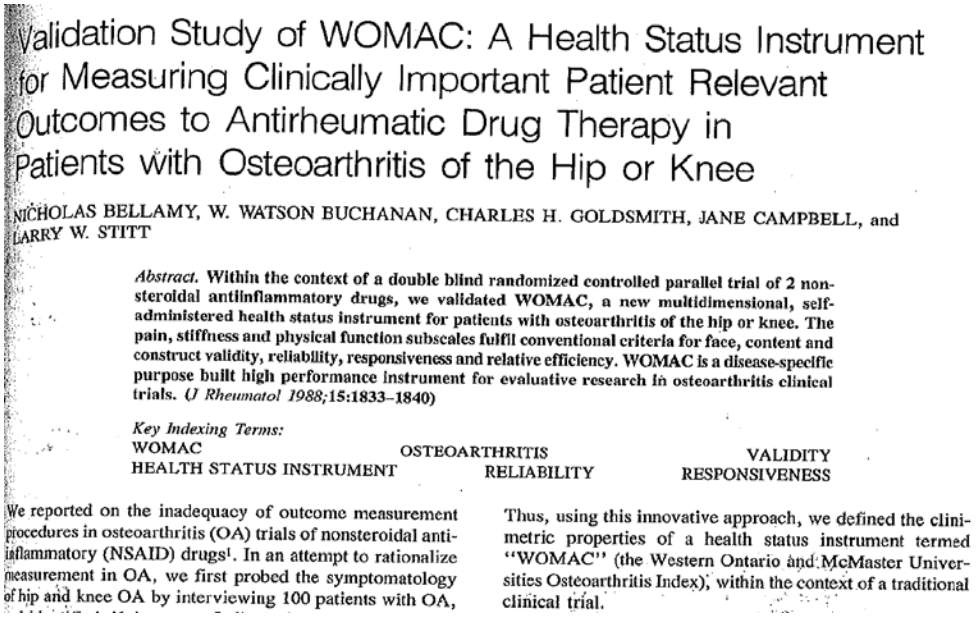
DESCRIPTION	SOLOMON STUDIES			EAASE PROJECT 1 – PROSPECTIVE OBSERVATIONAL COHORT					EAASE PROJECT 2 – RETROSPECTIVE LONGITUDINAL STUDY				
Setting	New Jersey and Pennsylvania			JJP, RVAMC, VACHS, Minn VAMC					USA				
Subjects	Low-income pharmaceutical assistance Medicare beneficiaries with history of osteoarthritis or rheumatoid arthritis			Veterans at study sites 2015-2018 with history of osteoarthritis of knee or hip					US veterans from 2010-2018 with history of osteoarthritis				
Cohorts	NSAID (ref)	opioid	coxib	NONE (ref)	NSAID	opioid	coxib	others	NONE (ref)	NSAID	opioid	coxib	others
Data sources:	Retrospective Medicare pharmaceutical data from low-income beneficiaries in New Jersey and Pennsylvania			National Retrospective VHA longitudinal administrative data **AND Prospective observational survey data**					National Retrospective VHA longitudinal administrative data				
Time points	Index date (Day 0), ~Day 7~Day 30 ~Day 60			Index date (Day 0),Day 30,Day 90, Day 180					Index date (Day 0), ~Day 7 ~Day 90 ~Day 30 ~Day 180 ~Day 60 ~1 year				
Effectiveness outcomes:	None			Baseline pain severity, Analgesic escalation, Self-reported effectiveness outcomes (**WOMAC,** patient global assessment of treatment, self report pain severity).					Baseline pain severity, Analgesic escalation,				

OUTCOME

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

WOMAC (Bellamy et al., J Rheumatology, 1988)

- Most commonly used self-administered assessment to evaluate knee and hip pain by orthopedists and rheumatologists, especially after surgeries or interventions.
- Traditional WOMAC made up of **24** Likert questions (0-4 scale) on stiffness, pain, and physical function



Validation Study of WOMAC: A Health Status Instrument for Measuring Clinically Important Patient Relevant Outcomes to Antirheumatic Drug Therapy in Patients with Osteoarthritis of the Hip or Knee

NICHOLAS BELLAMY, W. WATSON BUCHANAN, CHARLES H. GOLDSMITH, JANE CAMPBELL, and LARRY W. STITT

Abstract. Within the context of a double blind randomized controlled parallel trial of 2 non-steroidal antiinflammatory drugs, we validated WOMAC, a new multidimensional, self-administered health status instrument for patients with osteoarthritis of the hip or knee. The pain, stiffness and physical function subscales fulfil conventional criteria for face, content and construct validity, reliability, responsiveness and relative efficiency. WOMAC is a disease-specific purpose built high performance instrument for evaluative research in osteoarthritis clinical trials. *J Rheumatol 1988;*15:1833–1840)

Key Indexing Terms:
WOMAC OSTEOARTHRITIS VALIDITY
HEALTH STATUS INSTRUMENT RELIABILITY RESPONSIVENESS

We reported on the inadequacy of outcome measurement procedures in osteoarthritis (OA) trials of nonsteroidal anti-inflammatory (NSAID) drugs[1]. In an attempt to rationalize measurement in OA, we first probed the symptomatology of hip and knee OA by interviewing 100 patients with OA,

Thus, using this innovative approach, we defined the clinimetric properties of a health status instrument termed "WOMAC" (the Western Ontario and McMaster Universities Osteoarthritis Index), within the context of a traditional clinical trial.

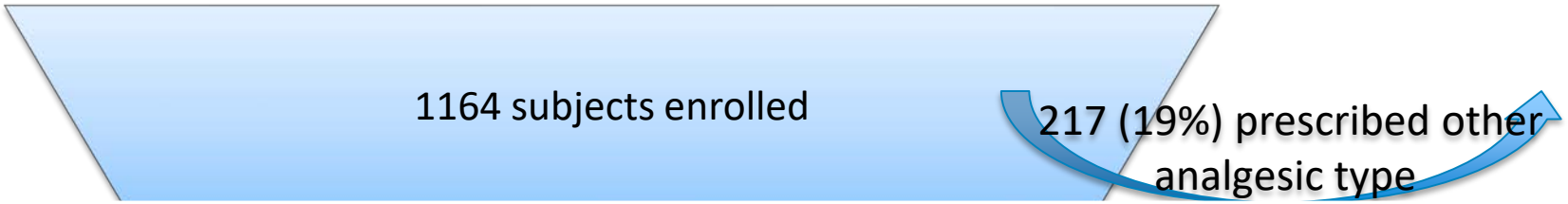
Effectiveness Outcome – Modified Short-Form WOMAC

- Modified Short-Form WOMAC includes Stiffness, Pain and *shorted* Function for total of **14** questions (Whitehouse, J Bone Joint Surg, 2003; Yang et al., J Bone Joint Surg, 2007)
- ***Lower WOMAC score = better***
- Minimal Clinically Important Differences (MCID) =
  - half SD change (Norman et al., Med Care, 2003)

Table I. Summary of the items scored in the Modified-short form WOMAC scale		
WOMAC domain	**WOMAC questions**	**Modified Short-Form WOMAC (Yang et. al.)**
Stiffness	Stiffness in the morning?	X
	Stiffness later in the day?	X
Pain	Pain while walking?	X
	Pain while climbing stairs?	X
	Pain at night?	X
	Pain while resting?	X
	Pain when putting weight on that knee or hip?	X
Function	How hard to go up stairs?	X
	How hard to rise from sitting?	X
	How hard to walk on flat ground?	X
	How hard to get in/out of a car?	X
	How hard to put your socks on?	X
	How hard to get out of bed?	X
	How hard to just sit?	X

RESULTS

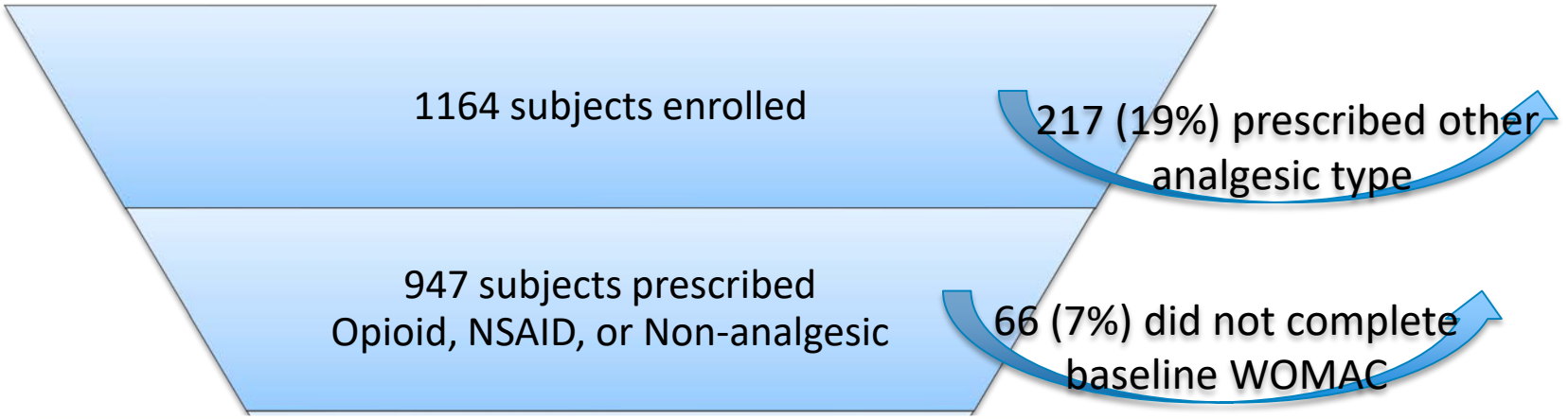
Prospective EAASE Cohort:



GRECC

Veterans Health Administration

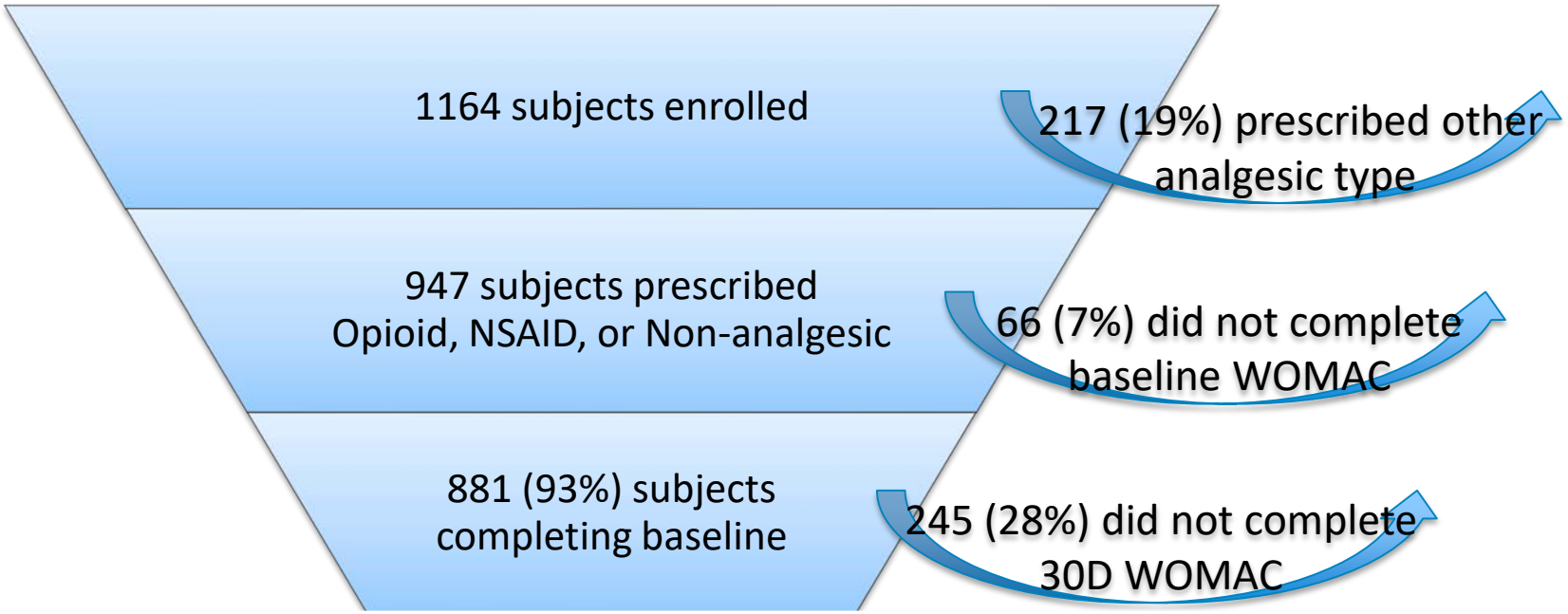
Prospective EAASE Cohort:



GRECC

Veterans Health Administration

Prospective EAASE Cohort:



GRECC

Veterans Health Administration

Prospective EAASE Cohort:

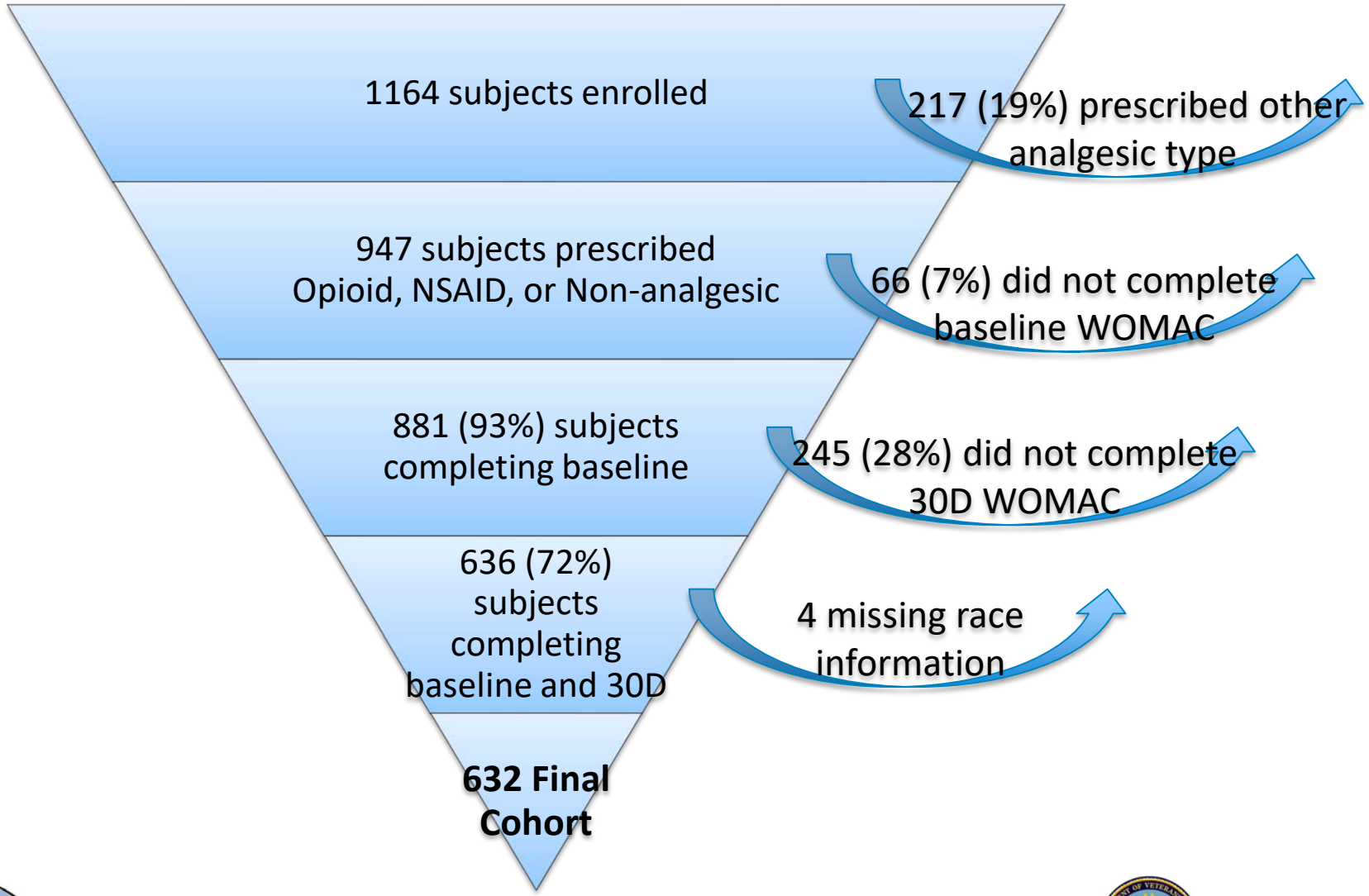


Table II. Presentation Cohort	
	N=632
Analgesic Category, n (%)	
Opioid	163 (25.7)
NSAID	256 (40.3)
Control	216 (34.0)
Age in years, median (IQR)	66.5 (67-71)
Male, n (%)	583 (91.8)
Race, n (%)	
White	524 (82.5)
Black	98 (15.4)
Other	13 (2.1)
Site, n (%)	
Bronx	52 (8.2)
Indianapolis	203 (32.0)
Minneapolis	300 (47.2)
West Haven	80 (12.6)

Table II. Presentation Cohort	
	N=632
Analgesic Category, n (%) Opioid NSAID Control	 **163 (25.7)** **256 (40.3)** **216 (34.0)**
Age in years, median (IQR)	66.5 (67-71)
Male, n (%)	583 **(91.8)**
Race, n (%) White Black Other	 524 **(82.5)** 98 (15.4) 13 (2.1)
Site, n (%) Bronx Indianapolis Minneapolis West Haven	 52 **(8.2)** 203 **(32.0)** 300 **(47.2)** 80 **(12.6)**

Table III. Comparison of covariates across drug category

	Opioids	NSAIDS	Controls	p-value
	n = 163	n = 253	n = 216	
Age, mean (SD)	66.2 (8.1)	64.7 (8.5)	68.6 (9.2)	<0.01
Male, n (%)	151 (92.6)	230 (90.9)	199 (92.1)	0.91
Race, n (%)				0.44
White	138 (84.7)	202 (79.8)	181 (83.8)	
Black	21 (12.9)	44 (17.4)	33 (15.3)	
Other	4 (2.5)	7 (2.8)	2 (0.9)	
Site, n (%)				0.61
Bronx	8 (4.9)	22 (8.7)	22 (10.2)	
Indianapolis	53 (32.5)	79 (31.2)	71 (32.9)	
Minneapolis	81 (49.7)	122 (48.2)	94 (43.5)	
West Haven	21 (12.9)	30 (11.9)	29 (13.4)	

Table IV. Mean (SD) WOMAC scores

	Opioids (n = 163)	NSAIDs (n = 253)	Controls (n = 216)
Pain Subscore			
Baseline Score	9.61 (4.41)	9.36 (4.08)	8.38 (4.32)
Score at 30D	9.44 (4.47)	9.11 (3.85)	8.52 (4.50)
Change	-0.18	-0.25	0.14
P-value	0.60	0.14	0.55
Stiffness Subscore			
Baseline Score	3.76 (1.87)	3.62 (1.77)	3.47 (1.92)
Score at 30D	3.56 (1.76)	3.80 (1.77)	3.35 (1.88)
Change	-0.20	0.17	-0.13
P-value	0.20	0.08	0.24
Function Subscore			
Baseline Score	11.61 (6.07)	11.52 (5.78)	10.41 (6.19)
Score at 30D	11.04 (5.79)	11.19 (5.68)	10.91 (6.42)
Change	-0.58	-0.33	0.50
P-value	**0.05***	0.18	**0.02***

**p <0.05, **p <0.01*

Minimal Clinically Important Difference (MCID) = ½ standard deviation REDUCTION in 30D score from baseline

Table V. Minimal Clinically Important Differences				
	Controls	Opioids	NSAIDs	p-value
Pain Subscore				
n (%) with MCID	71 (32.9)	52 (31.9)	83 (32.8)	0.98
Stiffness Subscore				
n (%) with MCID	72 (33.3)	40 (24.5)	55 (21.7)	0.02
Function Subscore				
n (%) with MCID	70 (32.4)	53 (32.5)	89 (35.2)	0.78

Bivariate results (Logistic Regression, MCID)

MCID = ½ SD reduction 30D from baseline	Pain MCID OR (95% CI)	p-value	Stiffness MCID OR (95% CI)	p-value	Function MCID OR (95% CI)	p-value
Control	ref	—	ref	—	ref	—
Opioid	0.96 (0.62, 1.48)	0.84	0.65 (0.41, 1.03)	0.06	1.00 (0.65, 1.55)	0.98
NSAID	1.00 (0.68, 1.47)	0.99	0.56 (0.37, 0.84)	**<0.01****	1.13 (0.77, 1.66)	0.53

**p <0.05, **p <0.01*

Adjusted Logistic Regression, MCID

MCID = ½ SD change baseline to 30D	Pain MCID OR (95% CI)	p-value	Stiffness MCID OR (95% CI)	p-value	Function MCID OR (95% CI)	p-value
Control	ref	—	ref	—	ref	—
Opioid	1.995 (1.09, 3.65)	**0.03***	0.87 (0.48, 1.59)	0.65	1.77 (0.97, 3.26)	0.07
NSAID	1.875 (1.09, 3.21)	**0.02***	0.63 (0.37, 1.07)	0.09	2.16 (1.24, 3.75)	**<0.01****

Subscores adjusted for age, gender, race, site location, baseline pain, baseline stiffness, and baseline function

*p <0.05 **p <0.01

SUMMARY & Early IMPLICATIONS

Summary

- Initiation of both opioids and NSAIDs are associated with clinically important differences in the improvement of pain in the 30D after baseline reported levels.
- NSAIDs appear to have a significant improvement in function at 30D, with a trend in function improvement for opioids.

Implications

- Short-term use of NSAIDs and opioids may improve both pain and function in older veterans with OA.
- Treatment of pain AND function as outcomes should be considered when evaluating impact of analgesic treatment.
- Initiation of analgesic types and evaluation of treatment outcomes are influenced by characteristics of the patient.

Next Steps

- Incorporate self-reported medications, additional variables about arthritis specificity, and other collected comorbidities
- Evaluate to see if these trends hold true over 90D and 180D follow-ups
- Other analgesics (acetaminophen, topicals)
- Better understand the specifics of these index medications (dosing, simultaneous prescriptions, rx length)
- Testing with alternate cutoffs for clinical significance

Limitations

- Confounding with selection bias for subjects and analgesic category treatment initially received
- Changes in dosing at baseline and follow-up
- Adherence to index medication

Future Studies

- Stay tuned for primary EAASE study results from full Project 1 prospective and Project 2 national cohort…

THANK YOU!!

PM: Tessa Runels
*Dorian Gittleman
*Kai Monde

Data: Erica Abel
Andrew Bean
Jessica Coffing
Jessica Lum
*Shubhada Sansgiry
*Dan Signor
*Lee Stefanis

Co-Is: Aaron Birnbaum
Ab Brody
Melissa Garrido
*Joan Penrod

Research Coordinators:
*Ruth Balk
*Rachel Dismore
Vera Gaetano
*David Leverty
*Brittany Majeski
*Eboni Manuel
Diana Natividad
*Grace Polusny
*Anthony Rinaldi

* No longer on study

And Thank YOU for your attention

Ula.Hwang@mountsinai.org
ula.hwang@va.gov

Adjusted Linear Regression

30D Scores	Pain Subscore	p-value	Stiffness Subscore	p-value	Function Subscore	p-value
Control	ref	—	ref	—	ref	—
Opioid	-0.06	0.83	-0.08	0.57	-0.91	**0.02***
NSAID	-0.27	0.30	0.20	0.12	-0.69	**0.04***

Subscores adjusted for age, gender, race, site location, baseline pain, baseline stiffness, and baseline function

**p <0.05, **p <0.01*

Model fit and CI

Recent Meta-analyses

- Recent evaluation of naproxen vs placebo over 7 days with investigator assessment of function found statistically significant reported of better rating of pain and function (Cuoto, Curr Med Res Opin, 2018) (pooled analyses of4-site multicenter secondary data)
- Meta analyses of pooled data: Opioid analgesics had a small effect on decreasing pain intensity (standardized mean difference = −.27; 95% CI = −.33 to −.20) and improving function (standardized mean difference = −.27, 95% CI = −.36 to −.18), which was not associated with daily dose or treatment duration. The odds of adverse events were 3 times higher (odds ratio = 2.94; 95% CI = 2.33–3.72) and the odds of treatment discontinuation due to adverse events 4 times higher (odds ratio = 4.04; 95% CI = 3.10–5.25) in patients treated with opioid analgesics. (Megale et al., J Pain, 2018)
- Another meta analyses: Improvement of function was larger in opioid-treated participants compared with control groups (SMD -0.26, 95% CI -0.35 to -0.17), which corresponds to a difference in function scores of 0.6 units between opioids and placebo on a standardised Western Ontario and McMaster Universities Arthritis Index (WOMAC) disability scale ranging from 0 to 10. This corresponds to a difference in improvement of 11% (95% CI 7% to 14%) between opioids (32% mean improvement from baseline) and placebo (21% mean improvement from baseline), which translates into an NNTB to cause one additional treatment response on function of 11 (95% CI 7 to 14). (da Costa et al., Cochran Database Syst, rev. 2014)

Recent studies

- 2 weeks of Cox-2 etoricoxib significantly improved WOMAC pain subscores (>30%), function (28%), and hyperalgesia. (Moss et.al. Osteoarthritis Cartilage 2017)
- Cochrane review of 36 trials from 1999-2014 comparing NSAIDs, celecoxib, placebo. Coxibs slightly better (4% improvement) than placebo and some NSAIDs in improving pain and function. Unable to assess harms secondary to risk of bias with pharma drug trials data. (Puljak, et.al. Cochrane Database Syst Rev 2017)