

# Daily MME Meta Analysis

Adapting a method recently developed by FDA to analyze a [related opioid methods question](#), we used meta analytic techniques to test the impact of the four definitions in the real-world. The general set up is to compare opioid use in FL vs. CA across the 4 definitions of daily MME. We previously observed that Florida had higher unadjusted levels of opioid use, presumably an interaction with an older population and the enactment of clinical pain management legislation. We took two approaches, 1) treating daily MME as categorical by comparing the proportion of "high dose" users among opioid recipients, and 2) comparing means of daily MME between the states in a continuous manner, stratified by medicines used for acute versus chronic pain.

```
In [7]: di "Stata MP"
version
di "Notebook generated on $$_DATE at $$_TIME ET"
```

Stata MP  
version 16.0  
Notebook generated on 26 May 2021 at 11:20:41 ET

## Comparing "High Dose" patients in CA and FL

Input dataset from table of high dose patients (>90 daily MME) among adult outpatient opioid recipients identified using the PDMP of each state.

```
In [2]: di "==== Proportion of high dose patients FL vs CA greater than 90 daily MME ====="
di "D1. Sum of days supply"
csi 87295 87078 1398296 2343792
di "D2. On-therapy days"
csi 136995 140822 1348596 2290048
di "D3. Defined observation window"
csi 97346 86407 1388245 2344463
di "D4. Maximum daily dose"
csi 211429 249471 1274162 2181399
```

==== Proportion of high dose patients FL vs CA greater than 90 daily MME =====

Definition 1

	Exposed	Unexposed	Total
Cases	87295	87078	174373
Noncases	1398296	2343792	3742088
Total	1485591	2430870	3916461
Risk	.0587611	.0358217	.0445231
	Point estimate		[95% Conf. Interval]
Risk difference	.0229394		.0224949 .0233839
Risk ratio	1.640376		1.625414 1.655475
Attr. frac. ex.	.3903837		1.3847723 .3959439
Attr. frac. pop	.1954347		
+-----+ chi2(1) = 11405.78 Pr>chi2 = 0.0000			

Definition 2

	Exposed	Unexposed	Total
Cases	136995	140822	277817
Noncases	1348596	2290048	3638644
Total	1485591	2430870	3916461
Risk	.0922158	.0579307	.0709357
	Point estimate		[95% Conf. Interval]
Risk difference	.0342851		.0337349 .0348353
Risk ratio	1.59183		1.580486 1.603256
Attr. frac. ex.	.3717922		1.3672831 .3762692
Attr. frac. pop	.1833353		
+-----+ chi2(1) = 16446.29 Pr>chi2 = 0.0000			

Definition 3

	Exposed	Unexposed	Total
Cases	97346	86407	183753
Noncases	1388245	2344463	3732708
Total	1485591	2430870	3916461
Risk	.0655268	.0355457	.0469181
	Point estimate		[95% Conf. Interval]
Risk difference	.0299811		.0295201 .0304421
Risk ratio	1.843451		1.827062 1.859988
Attr. frac. ex.	.4575392		1.4526731 .4623621
Attr. frac. pop	.2423885		
+-----+ chi2(1) = 18534.92 Pr>chi2 = 0.0000			

Definition 4

	Exposed	Unexposed	Total
Cases	211429	249471	460900
Noncases	1274162	2181399	3455561
Total	1485591	2430870	3916461
Risk	.1423198	.1026262	.1176828
	Point estimate		[95% Conf. Interval]
Risk difference	.0396936		.0390145 .0403727
Risk ratio	1.386778		1.379279 1.394318
Attr. frac. ex.	.2789041		1.2749835 .2828035
Attr. frac. pop	.1279419		
+-----+ chi2(1) = 13991.68 Pr>chi2 = 0.0000			

Scrape "Risk ratio" and CIs into new input dataset. Create log-transformed variables to meet normal distribution assumption of meta analytic statistics.

```
In [3]: clear all
qui: input definition irr ll ul str31 label
1 1.640376 1.625414 1.655475 "D1. Sum of days supply"
2 1.59183 1.580486 1.603256 "D2. Accounting for overlap days"
3 1.843451 1.827062 1.859988 "D3. Defined observation window"
4 1.386778 1.379279 1.394318 "D4. Maximum daily dose"
end
gen lnirr=ln(irr)
gen lnll=ln(ll)
gen lnul=ln(ul)
qui: meta set lnirr lnll lnul, studylabel(label)
```

```
. gen lnirr=ln(irr)
. gen lnll=ln(ll)
. gen lnul=ln(ul)
. qui: meta set lnirr lnll lnul, studylabel(label)
```

Run meta analysis command using fixed effects model. Since there is no sampling variation, fixed effects is the preferred *a priori* specification.

```
In [4]: meta summarize, fixed eform
```

```
Effect-size label: Effect Size
Effect size: lnirr
Std. Err.: _meta_se
Study label: label

Meta-analysis summary          Number of studies =      4
Fixed-effects model           Heterogeneity:
Method: Inverse-variance      I2 (%) = 99.91
                               H2 = 1085.83
```

Study	exp(ES)	[95% Conf. Interval]	% Weight
D1. Sum of days supply	1.640	1.625 1.655	15.27
D2. Accounting for overlap-s	1.592	1.580 1.603	25.06
D3. Defined observation wi-w	1.843	1.827 1.860	16.07
D4. Maximum daily dose	1.387	1.379 1.394	43.60
exp(theta)	1.542	1.536 1.547	

Test of theta = 0: z = 237.00 Prob > |z| = 0.0000  
Test of homogeneity: Q = chi2(3) = 3257.49 Prob > Q = 0.0000

For the sake of completeness, random effects models are also run, using the Sidik-Jonkman `random(sj)` estimator because tau is expected to be large [Veroniki et al.](#), with DerSimonian-Laird `random(dl)` as well separately for comparison, but fixed effects (above) is the more technically correct model specification.

```
In [5]: meta summarize, random(sj) eform
```

```
Effect-size label: Effect Size
Effect size: lnirr
Std. Err.: _meta_se
Study label: label

Meta-analysis summary          Number of studies =      4
Random-effects model           Heterogeneity:
Method: Sidik-Jonkman          tau2 = 0.0137
                               I2 (%) = 99.90
                               H2 = 954.41
```

Study	exp(ES)	[95% Conf. Interval]	% Weight
D1. Sum of days supply	1.640	1.625 1.655	24.99
D2. Accounting for overlap-s	1.592	1.580 1.603	25.00
D3. Defined observation wi-w	1.843	1.827 1.860	24.99
D4. Maximum daily dose	1.387	1.379 1.394	25.02
exp(theta)	1.607	1.433 1.803	

Test of theta = 0: z = 8.11 Prob > |z| = 0.0000  
Test of homogeneity: Q = chi2(3) = 3257.49 Prob > Q = 0.0000

```
In [6]: meta summarize, random(dl) eform
```

```
Effect-size label: Effect Size
Effect size: lnirr
Std. Err.: _meta_se
Study label: label

Meta-analysis summary          Number of studies =      4
Random-effects model           Heterogeneity:
Method: DerSimonian-Laird     tau2 = 0.0156
                               I2 (%) = 99.91
                               H2 = 1085.83
```

Study	exp(ES)	[95% Conf. Interval]	% Weight
D1. Sum of days supply	1.640	1.625 1.655	24.99
D2. Accounting for overlap-s	1.592	1.580 1.603	25.00
D3. Defined observation wi-w	1.843	1.827 1.860	24.99
D4. Maximum daily dose	1.387	1.379 1.394	25.01
exp(theta)	1.607	1.422 1.816	

Test of theta = 0: z = 7.61 Prob > |z| = 0.0000  
Test of homogeneity: Q = chi2(3) = 3257.49 Prob > Q = 0.0000

Results are similar, but SJ is preferred in Florida based on higher in Veroniki et al. The fixed effects model over emphasizes precision (e.g., confuses it for more information) in D4 due to the higher number of high dose patients. Since there is no sampling variation

## Interpretation

The proportion of "high dose" patients was consistently higher in Florida across all variants. However, the magnitude of the difference varied greatly: 84.3% (95% CI: 82.7%, 86.0%) for Definition 3 (defined observation window); 64.0% (95% CI: 62.5%, 65.5%) for Definition 1 (sum of days supply); 59.2% (95% CI: 58.0%, 60.3%) for Definition 2 (accounting for overlap days); and 38.7% (95% CI: 37.9%, 39.4%) for Definition 4 (maximum daily dose). Metrics confirmed very high heterogeneity between the definitions, with I2 greater than 99% and H2 of 1086, supported by tests of heterogeneity chi2 of 3257 on 3 degrees of freedom (p<0.0001), and overall effect z=237, with 1 degree of freedom and p<0.0001.

## Meta Analysis of Means by Type of Opioid

In this meta analysis we examine the impact of definitional variation on acute vs. chronic pain patients, measured by opioid formulation type. We stratified the sample into three sub-groups: 1) patients receiving on only immediate-release or short-acting opioids labeled for acute pain (hereafter immediate-release); 2) patients receiving only extended-release or long-acting opioids generally labeled for chronic pain (hereafter extended-release); and 3) patients receiving both immediate-release and extended-release opioids contemporaneously within the 3 month observation period (e.g., chronic pain patients receiving opioids for breakthrough pain or during taper).

Continuing with the approach in the previous meta analysis, we calculated mean differences in daily MME between Florida and California, treating each of the 4 daily MME definitions as separate studies run on the same sample (e.g., fixed effects).

### Immediate-release only

```
In [6]: clear
input definition n_fl m_fl sd_fl n_ca m_ca sd_ca
1 1338828 34.0531498 28.4797412 2273028 30.3156249 222.6063485
2 1338828 35.0964146 30.180772 2273028 31.5819604 223.0198312
3 1338828 12.5794512 25.2892396 2273028 10.3398905 42.5422362
4 1338828 44.7478467 48.3917948 2273028 39.6430507 280.3601706
end
qui: meta esize n_fl m_fl sd_fl n_ca m_ca sd_ca, esize(mdif)
meta summarize, fixed
```

```
definit- n_fl m_fl sd_fl n_ca m_ca sd_ca

Effect-size label: Mean Diff.
Effect size: _meta_es
Std. Err.: _meta_se

Meta-analysis summary          Number of studies =      4
Fixed-effects model           Heterogeneity:
Method: Inverse-variance      I2 (%) = 98.63
                               H2 = 72.98
```

Study	Mean Diff.	[95% Conf. Interval]	% Weight
Study 1	3.738	3.359 4.116	3.92
Study 2	3.514	3.135 3.894	3.90
Study 3	2.240	2.160 2.319	89.72
Study 4	5.105	4.626 5.584	2.45
theta	2.418	2.343 2.493	

Test of theta = 0: z = 63.18 Prob > |z| = 0.0000  
Test of homogeneity: Q = chi2(3) = 218.94 Prob > Q = 0.0000

### Extended-release only

```
In [7]: clear
input definition n_fl m_fl sd_fl n_ca m_ca sd_ca
2 26039 86.9302372 102.8249551 40038 90.2232825 100.0878302
3 26039 96.9367252 81.142005 40038 72.753132 104.6161615
4 26039 143.0437107 159.4875273 40038 153.6802569 205.2125971
end
qui: meta esize n_fl m_fl sd_fl n_ca m_ca sd_ca, esize(mdif)
meta summarize, fixed
```

```
definit-n n_fl m_fl sd_fl n_ca m_ca sd_ca

Effect-size label: Mean Diff.
Effect size: _meta_es
Std. Err.: _meta_se

Meta-analysis summary          Number of studies =      4
Fixed-effects model           Heterogeneity:
Method: Inverse-variance      I2 (%) = 86.38
                               H2 = 7.34
```

Study	Mean Diff.	[95% Conf. Interval]	% Weight
Study 1	-3.316	-4.806 -1.826	35.11
Study 2	-6.827	-8.745 -4.909	21.19
Study 3	-5.916	-7.415 -4.418	34.70
Study 4	-10.637	-13.578 -7.695	9.01
theta	-5.622	-6.504 -4.739	

Test of theta = 0: z = -12.48 Prob > |z| = 0.0000  
Test of homogeneity: Q = chi2(3) = 22.03 Prob > Q = 0.0001

### Both Extended-release and Immediate-release

```
In [8]: clear
input definition n_fl m_fl sd_fl n_ca m_ca sd_ca
1 120724 82.95423 59.1676551 117804 74.1906194 64.4024217
2 120724 160.1525421 131.6299812 117804 143.9839494 151.4652358
3 120724 133.0969773 125.945819 117804 122.7372442 148.5490438
4 120724 267.9496977 238.0130378 117804 250.7462218 282.0999741
end
qui: meta esize n_fl m_fl sd_fl n_ca m_ca sd_ca, esize(mdif)
meta summarize, fixed
```

```
definit-n n_fl m_fl sd_fl n_ca m_ca sd_ca

Effect-size label: Mean Diff.
Effect size: _meta_es
Std. Err.: _meta_se

Meta-analysis summary          Number of studies =      4
Fixed-effects model           Heterogeneity:
Method: Inverse-variance      I2 (%) = 98.34
                               H2 = 60.27
```

Study	Mean Diff.	[95% Conf. Interval]	% Weight
Study 1	8.764	8.267 9.260	69.06
Study 2	16.169	15.031 17.307	13.13
Study 3	10.360	9.255 11.464	13.94
Study 4	17.203	15.111 19.296	3.88
theta	10.286	9.873 10.698	

Test of theta = 0: z = 48.90 Prob > |z| = 0.0000  
Test of homogeneity: Q = chi2(3) = 180.81 Prob > Q = 0.0000

## Interpretation

- ER only group had lower mean daily MME in Florida than California?!
- Heterogeneity by I<sup>2</sup> was high for all 3 definitions
- Heterogeneity was lowest for ER-only group by both I<sup>2</sup> and X<sup>2</sup>
- For ER+IR group, the definitional variants would have resulted in us concluding that the average dose was 8.8 (8.3, 9.3) milligrams to 17.2 (15.1, 19.3) milligrams higher in Florida.