

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) comparing the proportion of "high dose" users among opioid recipients, and 2) comparing average daily MME between the states, stratified by medicines used for acute versus chronic pain.

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 [1]:

```
di "==== Proportion of high dose patients FL vs CA greater than 90 daily MME ====="
* definition 1
csi 87295 87078 1485591 2430870
* definition 2
csi 136995 140822 1485591 2430870
* definition 3
csi 97346 86407 1485591 2430870
* definition 4
csi 211429 249471 1485591 2430870

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

	Exposed	Unexposed	Total
Cases	87295	87078	174373
Noncases	1485591	2430870	3916461
Total	1572886	2517948	4090834
Risk	.0554999	.0345829	.0426253
	Point estimate	[95% Conf. Interval]	
Risk difference	.020917	.0204939	.02134
Risk ratio	1.604835	1.530811	1.619625
Attr. frac. ex.	.376883	.3711406	.3825731
Attr. frac. pop	.188676		
	chi2(1) = 10379.59	Pr>chi2 = 0.0000	

	Exposed	Unexposed	Total
Cases	136995	140822	277817
Noncases	1485591	2430870	3916461
Total	1622586	2571692	4194278
Risk	.08443	.0547585	.0662371
	Point estimate	[95% Conf. Interval]	
Risk difference	.0296715	.0291613	.0301818
Risk ratio	1.541862	1.537632	1.552692
Attr. frac. ex.	.3514334	.3467642	.3560692
Attr. frac. pop	.1732962		
	chi2(1) = 14161.57	Pr>chi2 = 0.0000	

	Exposed	Unexposed	Total
Cases	97346	86407	183753
Noncases	1485591	2430870	3916461
Total	1582937	2517277	4100214
Risk	.0614971	.0343256	.0448155
	Point estimate	[95% Conf. Interval]	
Risk difference	.0271715	.0267349	.0276081
Risk ratio	1.791581	1.775632	1.807674
Attr. frac. ex.	.4418339	.4368202	.446803
Attr. frac. pop	.2340684		
	chi2(1) = 16761.00	Pr>chi2 = 0.0000	

	Exposed	Unexposed	Total
Cases	211429	249471	460900
Noncases	1485591	2430870	3916461
Total	1697020	2680341	4377361
Risk	.1245884	.0930744	.1052917
	Point estimate	[95% Conf. Interval]	
Risk difference	.031514	.0309075	.0321206
Risk ratio	1.33859	1.331294	1.345926
Attr. frac. ex.	.2529453	.2488511	.2570171
Attr. frac. pop	.1160338		
	chi2(1) = 10954.62	Pr>chi2 = 0.0000	

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

In [2]:

```
clear all
qui: input definition irr ll ul str31 label
1 1.604835 1.590181 1.619625 "D1. Sum of days supply"
2 1.541862 1.530841 1.552962 "D2. Accounting for overlap days"
3 1.791581 1.775632 1.807674 "D3. Defined observation window"
4 1.33859 1.331294 1.345926 "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 REML model. Since there is no sampling variation, fixed effects is the preferred *a priori* specification.

In [3]:

```
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 = 1148.14

-----
Study |              exp(ES)    [95% Conf. Interval]    % Weight
-----+-----
D1. Sum of days supply |              1.605          1.590          1.620    15.37
D2. Accounting for overlap-s |              1.542          1.531          1.553    25.14
D3. Defined observation wi-w |              1.792          1.776          1.808    16.18
D4. Maximum daily dose |              1.339          1.331          1.346    43.31
-----+-----
exp(theta) |              1.495          1.490          1.501

Test of theta = 0: z = 219.17                                Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 3444.41                    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.

In [4]:

```
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 =    0.0145
                                                         I2 (%) =    99.90
                                                         H2 = 1004.19

-----
Study |              exp(ES)    [95% Conf. Interval]    % Weight
-----+-----
D1. Sum of days supply |              1.605          1.590          1.620    24.99
D2. Accounting for overlap-s |              1.542          1.531          1.553    25.00
D3. Defined observation wi-w |              1.792          1.776          1.808    24.99
D4. Maximum daily dose |              1.339          1.331          1.346    25.01
-----+-----
exp(theta) |              1.561          1.387          1.756

Test of theta = 0: z = 7.39                                Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 3444.41                    Prob > Q = 0.0000
```

In [5]:

```
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 =    0.0166
                                                         I2 (%) =    99.91
                                                         H2 = 1148.14

-----
Study |              exp(ES)    [95% Conf. Interval]    % Weight
-----+-----
D1. Sum of days supply |              1.605          1.590          1.620    24.99
D2. Accounting for overlap-s |              1.542          1.531          1.553    25.00
D3. Defined observation wi-w |              1.792          1.776          1.808    24.99
D4. Maximum daily dose |              1.339          1.331          1.346    25.01
-----+-----
exp(theta) |              1.561          1.376          1.771

Test of theta = 0: z = 6.91                                Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(3) = 3444.41                    Prob > Q = 0.0000
```

Results are similar, but SJ is preferred based on simulations 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: 79% (95% CI: 78%, 81%) for Definition 3 (defined observation window); 60% (95% CI: 59%, 62%) for Definition 1 (sum of days supply); 54% (95% CI: 53%, 55%) for Definition 2 (accounting for overlap days); and 34% (95% CI: 33%, 35%) for Definition 4 (maximum daily dose). Metrics confirmed very high heterogeneity between the definitions, with I2 greater than 99% and H2 of 1148, supported by tests of heterogeneity chi2 of 3444 on 3 degrees of freedom (p<0.0001), and overall effect z=219, 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).

Meta regression is being used to assess heterogeneity, not to derive a summary effect measure. Since there is no sampling variation between studies, fixed effect models are used.

Continuing with the approach in the previous meta analysis, we compared the average daily MME between Florida and California. We calculate difference in means, by definition.

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(mdiff)
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 (%) =	98.63			
		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
1 26039 86.9071545 87.9504585 40038 90.2232825 100.0878302
2 26039 96.9302372 102.8249551 40038 103.7573329 134.372793
3 26039 66.8367252 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(mdiff)
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(mdiff)
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 I² was high for all 3 definitions
- Heterogeneity was lowest for ER-only group by both I² and X²
- 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.