Supplemental materials for:

Scherrer JF, Salas J, Copeland LA, et al. Prescription opioid duration, dose, and increased risk of depression in 3 large patient populations. *Ann Fam Med.* 2016;14(1):54-62.

SUPPLEMENTAL APPENDIX 1.

e-Table 1. Association (%) of opioid exposure and covariates with incident depression

	VA		BSWH		HFHS	
	Depression		**Depression**		**Depression**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**
Exposure/covariates, n(%)	**(n=62,385)**	**(n=8,612)**	**(n=12,580)**	**(n=1,197)**	**(n=20,390)**	**(n=2,591)**
Age (mean, sd)	56.3(±12.9)	48.9 (±11.8)[a]	44.7 (±15.0)	43.5 (±15.1)[b]	47.7 (±14.4)	47.7 (±14.4)
Gender: male	94.6	89.5[a]	38.9	22.4[a]	41.6	26.2[a]
Race						
White	76.2	72.4[a]	68.7	75.4[a]	45.6	53.7[a]
Insurance						
VA only	64.0	73.1[a]	--	--	--	--
Medicare	--	--	13.3	14.8	0.8	0.3[b]
Marital status						
Married	55.9	49.1[a]	--	--	--	--
Opioid duration (days)						
1-30	78.4	74.5[a]	93.3	90.1[a]	89.8	84.3[a]
31-90	12.0	13.7	5.4	6.8	7.0	9.7
> 90	9.7	11.8	1.3	3.1	3.2	6.0
Last MED dose (mg)^						
1-50	94.0	92.2[a]	93.5	94.1	87.0	87.4
51-100	5.0	6.0	5.2	4.5	11.5	10.9
>100	1.0	1.8	1.3	1.4	1.5	1.7
Psychiatric comorbidities[#]						
PTSD	13.7	21.1[a]	0.2	1.1[a]	0.4	1.9[a]
Other anxiety ^^	10.9	18.1[a]	4.3	19.5[a]	6.8	26.2[a]
Nicotine dependence/ history of smoking	42.0	46.3[a]	7.9	6.9	22.3	28.2[a]
Alcohol abuse/dependence	19.0	28.6[a]	1.6	3.1[a]	4.2	6.3[a]
Any illicit drug abuse/dependence	11.0	21.4[a]	0.6	1.8[a]	2.5	4.9[a]
Metabolic/Cardiovasc comorbidities[#]						
Diabetes Type II	43.4	33.7[a]	20.2	15.6[a]	31.1	29.1[c]
Hypertension	84.0	72.0[a]	20.2	46.9[c]	69.1	68.2
Cardiovascular disease ##	87.9	76.2[a]	3.7	56.2[c]	76.2	73.6[b]

Cerebrovascular disease	22.1	13.6[a]	50.0	12.3[b]	15.1	18.4[a]
Obesity diagnosis	39.0	38.5	59.5	22.1[b]	28.3	29.3
Other comorbidities [#]						
Low T	3.1	2.7[c]	1.7	0.7[c]	1.4	0.9[c]
Sleep apnea	10.8	9.4[a]	8.4	11.9[a]	6.9	7.1
Painful conditions [#]						
Arthritis	82.5	81.4[b]	61.9	62.7	80	79.9
Back pain	65.0	69.9[a]	52.8	57.3[b]	69.1	70.8
Headaches	19.3	27.1[a]	25.5	35.8[a]	35.9	41.3[a]
Musculoskeletal pain	62.9	64.8[b]	66.3	67.8	84.0	82.9
Neuropathic pain	32.6	30.9[b]	17	20.6[b]	22.4	24.9[b]
Maximum pain score, (mean, sd)	8.3 (±2.2)	9.2 (±1.4)[a]	--	--	--	--
Healthcare utilization						
> 75th percentile	24.9	47.0[a]	25.9	20[a]	22.1	18.8[a]

a: p<0.001, b: p<0.01, c: p<0.05

[^] Opioid morphine equivalent dose (MED) at end of follow-up defined by incident depression, end or incident opioid prescription or last available observation, [#] Comorbidities occurring before incident depression

[^^] Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

[##] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

SUPPLEMENTAL APPENDIX 1.

e-Table 2. Association (%) of incident depression and covariates with opioid use duration

Outcome/covariates,	VA opioid use duration			BSWH opioid use duration			HFHS opioid use duration		
	1-30 days (n=55,306)	31-90 days (n=8,640)	> 90 days (n=7051)	1-30 days (n=12,817)	31-90 days (n=765)	> 90 days (n=195)	1-30 days (n=20,487)	31-90 days (n=1,685)	> 90 days (n=809)
Age, mean (sd)	55.2(±13.1)	55.9(±13.0)	56.0(±12.5)[a]	44.1 (±14.9)	49.6 (±15.2)	59.7 (±15.4) [a]	47.2 (±14.3)	51.8 (±14.3)	54.3 (±13.8)[a]
Gender: male	93.7	94.2	95.6[a]	37.4	40.3	32.3	40.1	38.7	37.8
Race									
White	74.5	77.1	84.0[a]	68.8	74.4	82.1[a]	46.5	47.7	44.1[a]
Insurance									
VA only	65.4	65.0	62.6[a]	--	--	--	--	--	--
Medicare	--	--	--	12.3	22.1	51.3[a]	141 (0.7)	20 (1.2)	9 (1.1)[c]
Marital status									
Married	54.8	55.1	56.6[c]	--	--	--	--	--	--
Incident depression	11.6	13.6	14.4[a]	8.4	10.6	19.0[a]	10.7	14.8	19.3[a]
Last MED dose (mg)^									
1-50	94.0	95.5	90.6[a]	94	90.2	81.5[a]	86.6	90.5	91.2[a]
51-100	5.1	3.7	7.0	4.7	8.6	16.4	11.8	8.7	6.9
>100	1.0	0.8	2.4	1.3	1.2	2.1	1.6	0.8	1.9
Psychiatric comorbidities [#]									
PTSD	14.1	15.2	17.3[a]	0.2	0.8	1[a]	0.5	1.0	1.0[b]
Other anxiety [^^]	11.1	13.1	15.7[a]	5.4	7.5	9.7[b]	8.7	11.6	11[a]
Nicotine abuse/dependence	41.5	44.4	48.2[a]	7.6	9.4	11.8[c]	21.8	31.4	35.7[a]
Alcohol abuse/dependence	19.8	21.5	21.3[a]	1.7	2.0	3.6	4.1	6.4	7.4[a]
Any illicit drug abuse/dependence	12.0	12.7	14.0[a]	0.7	0.8	4.6[a]	2.4	4.9	7.5[a]
Metabolic/Cardiovasc comorbidities [#]									
Diabetes Type II	41.7	43.5	44.2[a]	19.3	26.1	30.8[a]	30.1	35.6	41.4[a]
Hypertension	82.1	83.5	85.3[a]	48.5	61.4	79.5[a]	67.7	77.1	85.2[a]

Cardiovascular disease [##]	86.2	87.1	87.9[a]	58.3	70.7	75.9[a]	75.1	81.5	83.9[a]
Cerebrovascular disease	20.8	22.7	21.1[b]	9.2	17.7	26.7[a]	14.7	19.8	26.0[a]
Obesity diagnosis	38.8	39.8	38.8	19.2	18.3	22.6	27.9	31.5	33.0[a]
Other comorbidities [#]									
Low T	3.0	2.8	4.0[a]	1.6	2.0	0.5	1.4	0.9	1.5
Sleep apnea	10.6	11.3	10.2	8.5	10.9	10.8[c]	6.6	9.7	7.5[a]
Painful conditions [#]									
Arthritis	81.4	85.0	86.8[a]	60.7	77.7	83.6[a]	78.9	88.5	89.6[a]
Back pain	63.7	69.6	76.0[a]	52.0	64.4	82.6[a]	67.9	79.7	82.8[a]
Headaches	20.3	21.0	19.4	26.2	28.4	31.3	36.5	36.7	36.6
Musculoskeletal pain	63.0	65.6	61.4[a]	65.5	77.1	83.6[a]	83.1	89.9	91.4[a]
Neuropathic pain	31.3	35.2	37.4[a]	16.8	22.5	30.8[a]	21.7	29.1	35.1[a]
Maximum pain score, mean (sd)	8.3 (±2.2)	8.7 (±1.9)	8.7(±1.9)[a]	--	--	--	--	--	--
High Healthcare utilization > 75th percentile	27.2	30.1	27.9[a]	25.5	24.2	22.6[a]	21.8	20.1	23.1[c]

a: p<0.001, b: p<0.01, c: p<0.05

[^] Opioid morphine equivalent dose (MED) at end of follow-up defined by incident depression, end or incident opioid prescription or last available observation, [#] Comorbidities occurring before incident depression

[^^] Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

[##] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

SUPPLEMENTAL APPENDIX 1.

e-Table 3. Distribution (%) of incident depression and covariates with last opioid morphine equivalent dose

Outcome/covariates,	VA patients			BSWH patients			HFHS patients		
	1-50 mg (n=66,601)	51-100 mg (n=3,613)	> 100 mg (n=783)	1-50 mg (n=12,893)	51-100 mg (n=706)	> 100 mg (n=178)	1-50 mg (n=20,006)	51-100 mg (n=2,628)	> 100 mg (n=347)
Age (mean, (SD))	55.5 (±13.0)	54.0 (±12.4)	51.5 (±11.6)[a]	44.4 (±15.0)	48.7 (±15.1)	45.3 (±14.7)	47.7 (±14.5)	47.9 (±13.8)	46.3 (±14.9)[c]
Gender: male	93.9	94.7	94.8	37.0	47.5	33.2[a]	39.8	41.2	37.5
Race									
White	75.6	78.6	79.7[a]	69	73.7	71.4[c]	46.3	48.7	44.4
Insurance									
VA only	64.8	68.1	71.4[a]	--	--	--	--	--	--
Medicare	--	--	--	12.8	24.1	16.3[a]	0.7	1.0	0.6
Marital status									
Married	55.3	51.8	52.4[a]	--	--	--	--	--	--
Incident depression	11.9	14.2	20.1[a]	8.7	7.7	9.6	11.3	10.8	12.4
Opioid duration (days)									
1-30	78.0	77.4	69.4[a]	93.4	86.1	92.7[a]	88.7	92.3	91.6[a]
31-90	12.4	8.9	8.8	5.4	9.4	5.1	7.6	5.6	4.0
>90	9.6	13.7	21.8	1.2	4.5	2.3	3.7	2.1	4.3
Psychiatric comorbidities[#]									
PTSD	14.4	15.8	21.5[a]	0.2	0.6	0 (0)	0.5	0.7	0.3
Other anxiety [^^]	11.7	12.6	16.6[a]	5.5	6.0	9.0	9.1	8.0	7.2
Nicotine dependence/ histor of smoking	42.3	45.0	52.2[a]	7.7	8.2	8.4	22.6	24.6	28.5[b]
Alcohol abuse/ dependence	19.9	22.9	27.2[a]	1.7	1.8	0.6	4.4	4.4	2.9
Any illicit drug abuse/dependence	12.1	14.9	19.4[a]	0.7	0.4	1.1	2.7	2.7	2.3
Metabolic/Cardiovasc comorbidities[#]									
Diabetes Type II	42.2	41.8	42.8	19.7	22.0	19.7	30.9	31.9	25.9
Hypertension	82.6	82.4	81.7	49.2	59.4	47.2[a]	69	69.3	69.5
Cardiovascular disease [##]	86.5	87.1	83.7[c]	58.7	68	62.9[a]	75.6	78.6	76.1[b]
Cerebrovascular disease	21.1	19.6	19.8	9.7	14.6	9.0[a]	15.4	16.1	15.9
Obesity diagnosis	38.8	40.5	39.3	19.1	18.0	25.8	28.2	28.2	38.9[a]
Other comorbidities[#]									

Low T	3.0	3.4	5.8[a]	1.6	1.8	0.6	1.4	1.2	0.3
Sleep apnea	10.5	12.3	12.6[a]	8.4	11.1	17.4[a]	6.7	7.3	12.1[b]
Painful conditions [#]									
Arthritis	82.4	82.0	84.2	61.6	69.4	60.1[a]	79.8	82.0	77.2[c]
Back pain	65.4	67.4	77.8[a]	53.0	56.0	55.1	69.8	65.9	65.4[a]
Headaches	20.2	21.4	24.8[a]	26.5	21.7	31.5[b]	36.7	34.8	38.3
Musculoskeletal pain	62.8	67.1	70.4[a]	66.1	71.7	68.0[b]	83.9	83.6	81.0
Neuropathic pain	32.2	34.8	38.4[a]	17.2	20.7	19.1[c]	22.6	23.2	20.8
Maximum pain score, mean (sd)	8.4 (±2.2)	8.6 (±2.1)	9.1 (±1.8)[a]	--	--	--			
Healthcare utilization									
> 75th percentile	27.2	32.3	39.1[a]	25.6	20.4	28.1	21.6	22.0	22.8[b]

a: p<0.001, b: p<0.01, c: p<0.05

[^] Opioid morphine equivalent dose (MED) at end of follow-up defined by incident depression, end or incident opioid prescription or last available observation, [#] Comorbidities occurring before incident depression

[^^]Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

[##]Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

SUPPLEMENTAL APPENDIX 1.

e. Table 4. Distribution (%) of covariates by duration of opioid use after balancing by weighted inverse probability of duration exposure

Covariates	VA opioid duration			BSWH opioid duration			HFHS opioid duration		
	1-30 days (n=55,306)	31-90 days (n=8,640)	> 90 days (n=7,051)	1-30 days (n=12,817)	31-90 days (n=765)	> 90 days (n=195)	1-30 days (n=20,487)	31-90 days (n=1,685)	> 90 days (n=808)
Age, mean (sd)	55.4 (±13.0)	55.5 (±13.0)	55.6 (±12.9)	44.60 (±15.0)	44.29 (±15.4)	46.50 (±13.5)	47.74 (±14.4)	47.67 (±14.6)	48.96 (±13.6)
Gender: male	93.9	93.9	94.1	37.47	36.11	45.84	39.92	40.55	42.25
Race									
White	75.8	75.7	76.0	72.40	72.06	76.00	47.20	46.57	46.85
Insurance									
VA only	65.1	64.8	65.3	--	--	--	--	--	--
Marital status									
Married	55.1	55.4	55.1	--	--	--	--	--	--
Last MED dose (mg)^									
1-50	93.8	94.0	94.1	93.58	93.68	92.69	87.06	86.85	87.36
51-100	5.1	4.9	4.8	5.13	5.23	6.01	11.43	11.60	11.21
>100	1.1	1.1	1.0	1.29	1.09	1.30	1.51	1.54	1.43
Psychiatric comorbidities [#]									
PTSD	14.6	14.5	14.8	0.25	0.17	0.41	0.54	0.63	0.51
Other anxiety [^^]	11.8	11.7	11.8	5.60	5.28	6.95	8.95	9.39	9.29
Nicotine dependence/ history of smoking	42.5	42.5	42.8	7.76	7.89	6.02	22.98	22.86	25.08
Alcohol abuse/dependence	20.2	20.1	20.6	1.71	1.78	2.06	4.41	4.60	4.98
Any illicit drug abuse/dependence	12.3	12.3	12.3	0.75	0.58	0.54	2.73	2.74	3.60
Metabolic/Cardiovasc comorbidities [#]									
Diabetes Type II	42.2	42.2	42.9	19.84	20.02	23.68	30.91	30.15	32.66
Hypertension	82.6	82.6	83.1	49.68	48.42	58.12	69.02	68.82	71.85
Cardiovascular disease [##]	86.5	86.5	86.7	59.21	56.66	55.56	75.91	75.46	78.21
Cerebrovascular disease	21.0	21.1	21.2	9.96	10.13	11.04	15.50	15.59	16.53
Obesity diagnosis	38.9	38.7	39.4	19.15	18.50	21.79	28.38	28.54	30.16
Other comorbidities [#]									
Low T	3.1	3.0	3.1	1.59	1.41	0.64	1.36	1.28	1.15

Sleep apnea	10.7	10.6	10.9	8.67	8.40	10.92	6.90	7.26	7.40
Painful conditions [#]									
Arthritis	82.4	82.6	83.3	61.98	61.42	69.09	79.99	80.19	81.82
Back pain	65.6	65.8	66.0	53.15	52.58	66.07[b]	69.27	69.47	70.32
Headaches	20.3	20.4	20.3	26.35	26.38	32.14	36.53	37.28	36.79
Musculoskeletal pain	63.1	63.1	63.9	66.41	65.71	61.48	83.87	83.39	84.76
Neuropathic pain	32.4	32.4	32.7	17.37	16.96	24.49	22.70	22.95	25.39
Maximum pain score, mean(sd)	8.4 (±2.2)	8.4 (±2.1)	8.4 (±2.1)	--	--	--	--	--	--
Healthcare utilization									
> 75th percentile	27.6	27.6	28.7	25.33	24.17	20.91	21.68	22.28	22.39

a: p<0.001, b: p<0.01, c: p<0.05

[^] Opioid morphine equivalent dose (MED) at end of follow-up defined by incident depression, end or incident opioid prescription or last available observation, [#] Comorbidities occurring before incident depression

[^^] Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

[##] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction

SUPPLEMENTAL APPENDIX 1.

e. Table 5. Distribution (%) of covariates by last opioid morphine equivalent dose after balancing by weighted inverse probability of dose exposure.

Covariates, %	VA patients 1-50 mg (n=66,601)	VA patients 51-100 mg (n=3,613)	VA patients > 100 mg (n=783)	BSWH patients 1-50 mg (n=12,893)	BSWH patients 51-100 mg (n=706)	BSWH patients > 100 mg (n=178)	HFHS patients 1-50 mg (n=20,006)	HFHS patients 51-100 mg (n=2,628)	HFHS patients > 100 mg (n=347)
Age, mean (sd)	55.4 (±13.0)	55.4 (±13.0)	55.9 (±13.2)	44.6 (±15.1)	44.9 (±15.1)	45.0 (±15.4)	47.7 (±14.5)	47.7 (±13.9)	47.9 (±15.2)
Gender: male	93.9	93.9	94.4	37.48	37.74	39.24	39.89	39.72	39.01
Race									
White	75.8	75.5	73.2	72.37	73.93	71.73	47.18	47.37	45.84
Insurance									
VA only	65.1	65.4	64.4	--	--	--	--	--	--
Marital status									
Married	55.0	54.5	56.4	--	--	--	--	--	--
Opioid duration (days)									
1-30	77.9	77.9	78.0	93.03	92.97	92.35	89.15	89.25	88.17
31-90	12.2	12.3	12.6	5.55	5.57	6.10	7.33	7.26	8.04
>90	9.9	9.8	9.4	1.42	1.46	1.56	3.52	3.49	3.79
Psychiatric comorbidities [#]									
PTSD	14.6	14.6	14.5	0.25	0.19	0.00	0.54	0.55	0.43
Other anxiety [^^]	11.8	11.9	12.6	5.60	6.38	5.00	8.95	8.96	9.53
Nicotine dependence/ history of smoking	42.5	42.5	40.7	7.77	7.54	7.08	22.95	22.76	24.56
Alcohol abuse/dependence	20.2	20.6	20.1	1.70	1.78	1.14	4.40	4.42	4.76
Any illicit drug abuse/dependence	12.3	12.3	11.6	0.73	0.94	0.15	2.72	2.76	2.14
Metabolic/Cardiovasc comorbidities [#]									
Diabetes Type II	42.2	42.4	44.2	19.83	19.74	20.20	30.90	31.12	32.28
Hypertension	82.6	82.7	82.1	49.69	50.11	51.33	69.01	69.28	70.64
Cardiovascular disease [##]	86.4	86.4	86.3	59.24	59.78	59.78	75.90	75.86	75.27
Cerebrovascular disease	21.0	21.0	22.8	9.95	10.58	12.55	15.49	15.54	14.13
Obesity diagnosis	38.9	39.0	39.0	19.16	18.91	18.51	28.38	28.52	28.51
Other comorbidities [#]									

Low T	3.1	3.0	2.4	1.59	1.54	2.41	1.36	1.34	0.57
Sleep apnea	10.7	10.8	11.4	8.68	9.45	9.50	6.89	6.95	7.14
Painful conditions[#]									
Arthritis	82.4	82.2	80.9	61.98	62.44	63.57	79.98	79.80	79.97
Back pain	65.6	65.2	62.4	53.15	52.13	55.52	69.25	69.30	69.17
Headaches	20.3	20.3	21.6	26.36	26.89	29.15	36.51	36.25	36.57
Musculoskeletal pain	63.1	63.2	62.8	66.41	67.02	68.18	83.87	83.92	84.36
Neuropathic pain	32.4	32.4	29.8	17.35	17.16	19.95	22.68	22.74	23.57
Maximum pain score, mean(sd)	8.4 (±2.2)	8.4 (±2.2)	8.3 (±2.3)	--	--	--	--	--	--
Healthcare utilization									
> 75th percentile	27.6	27.7	26.4	25.34	25.18	24.84	21.68	21.72	22.96

a: $p<0.001$, b: $p<0.01$, c: $p<0.05$

[^] Opioid morphine equivalent dose (MED) at end of follow-up defined by incident depression, end or incident opioid prescription or last available observation, [#] Comorbidities occurring before incident depression

[^^] Other anxiety disorders = panic disorder, OCD, social phobia, GAD, Anxiety NOS

[##] Cardiovascular disease = hyperlipidemia, ischemic heart disease, diseases of pulmonary circulation, other heart disease, hypertensive heart disease, myocardial infarction