

Online Supplement

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Supplementary Table S1. International Classification of Disease diagnosis codes for clinical conditions of interest

Conditions	ICD-9 Codes	ICD-10 Codes
Major Depression	296.2x, 296.3x	F32, F32.0, F32.1, F32.2, F32.3, F32.4, F32.5, F32.9, F33, F33.0, F33.1, F33.2, F33.3, F33.4, F33.40, F33.41, F33.42, F33.8, F33.9
PTSD	309.81	F43.1, F43.10, F43.11, F43.12
Other Anxiety	300.00, 300.01, 300.02, 300.09, 300.10, 300.20, 300.21, 300.22, 300.23, 300.29	F06.4, F40, F40.0, F40.00, F40.01, F40.02, F40.1, F40.10, F40.11, F40.2, F40.21, 40.22, F40.23, F40.24, F40.29, F40.8, F40.9, F41, F41.0, F41.3, F41.8, F41.9, F42, F43, F43.0, F43.8, F43.9, F45.2, F45.20, F45.21, F45.29, R45.7
Alcohol-related disorder	303.0x, 303.9x, 305.0x	F10.1X, F10.2X, F10.9x
Non-alcohol substance-related disorder		
Opioid	304.0x, 304.7x, 305.5x, excluding 304.03, 304.73, 305.53	F11.1X, F11.2X
Cocaine/Stimulants	304.2x, 304.4x, 305.6x, 305.7x	F14.1X, F14.2X, F14.9X, F15.1X, F15.2X, F15.9X
Sedatives	304.1x, 305.4x	F13.1X, F13.2X, F13.9X
Cannabis	304.3x, 305.2x	F12.1X, F12.2X, F12.9X
Other	304.5x, 304.6x, 304.8x, 304.9x, 305.3x, 305.8x, 305.9x	F16.1X, F16.2X, F16.9X, F18.1X, F18.2X, F18.9X, F19.1X, F19.2X, F19.9X
Dementia	290.0, 290.1x, 290.2x, 290.3, 294.10, 294.11, 331.0, 290.4x, 291.2, 331.1x, 331.82, 294.20, 294.21	F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, F10.27, G30.0, G30.1, G30.8, G30.9, G31.01, G31.09, G31.1, G31.83
Insomnia	307.4x, 327.00, 327.01, 327.02, 327.09, 780.51, 780.52	G47.00, G47.01, G47.09
Chronic Pain	256.60, 307.80, 307.81, 307.89, 346.0-346.9, 355.0, 355.9, 356.0, 357.2, 357.9, 710.0-739.9, 784.0	<p>We used the following <i>ICD-9-CM</i> non-cancer chronic pain scheme, after Ilgen et al.¹</p> <ul style="list-style-type: none"> • back pain (720.0-724.9) • arthritis (710.0-739.9, excluding back pain codes) • migraines (346.0-346.9) • headache or tension headache (784.0 and 307.81) • psychogenic pain (307.80 and 307.89) • neuropathy (256.60, 355.0, 355.9, 356.0, 357.2, and 357.9) • fibromyalgia (729.1) <p>We used the ICD-9 to -10 crosswalk from CMS² to identify the equivalent ICD-10 codes. The full list of equivalent ICD-10 codes is available from the authors here.³</p>

¹ Ilgen MA, Kleinberg F, Ignacio RV, et al. Noncancer pain conditions and risk of suicide. *JAMA Psychiatry*. 2013;70(7):692-697.

² <https://data.nber.org/data/icd9-icd-10-cm-and-pcs-crosswalk-general-equivalence-mapping.html>

³ <https://umich.box.com/s/gj3wjk6sx64wg02t17l4uq9xnfooyrbr>

Supplementary Table S2. Monthly denominator, numerator, and prevalence of benzodiazepine use and benzodiazepine-opioid co-prescribing in a Medicare population, 2013 to 2017

Year	Month	Denominator	BZD		BZD-opioid	
			Numerator	Prevalence (%)	Numerator	Prevalence (%)
2013	jan	3580268	263303	7.35	97999	2.74
	feb	3581848	350501	9.79	135187	3.77
	mar	3582517	373244	10.42	143814	4.01
	apr	3596204	374387	10.41	143607	3.99
	may	3591043	372202	10.36	144430	4.02
	jun	3596177	370359	10.30	142719	3.97
	jul	3609321	376906	10.44	145540	4.03
	aug	3615462	380897	10.54	147335	4.08
	sep	3619097	380264	10.51	145978	4.03
	oct	3621826	386800	10.68	149499	4.13
	nov	3620651	381680	10.54	146227	4.04
	dec	3618370	382813	10.58	146215	4.04
2014	jan	3717915	401549	10.80	154476	4.15
	feb	3721698	399640	10.74	152271	4.09
	mar	3725546	403109	10.82	154486	4.15
	apr	3728305	400023	10.73	152703	4.10
	may	3727049	399064	10.71	153303	4.11
	jun	3734127	396301	10.61	151392	4.05
	jul	3728865	398579	10.69	153265	4.11
	aug	3736396	397848	10.65	152336	4.08
	sep	3741128	398202	10.64	150897	4.03
	oct	3743835	404821	10.81	152481	4.07
	nov	3743616	395230	10.56	145398	3.88
	dec	3738222	397961	10.65	146127	3.91
2015	jan	4073791	438362	10.76	161473	3.96
	feb	4078722	439408	10.77	160451	3.93
	mar	4080494	447172	10.96	164640	4.03
	apr	4072697	446082	10.95	164720	4.04
	may	4070477	439791	10.80	162223	3.99
	jun	4077095	438329	10.75	161015	3.95
	jul	4092072	443185	10.83	163410	3.99
	aug	4099203	438991	10.71	161365	3.94
	sep	4105612	439491	10.70	161176	3.93
	oct	4112270	443514	10.79	162739	3.96
	nov	4114278	436296	10.60	158091	3.84
	dec	4114255	440054	10.70	160141	3.89
2016	jan	3955537	421579	10.66	155270	3.93
	feb	3960855	419978	10.60	153941	3.89
	mar	3970820	424712	10.70	156426	3.94
	apr	3969341	419089	10.56	153274	3.86
	may	3969066	414636	10.45	150904	3.80
	jun	3973505	413302	10.40	149712	3.77

	jul	3992253	409645	10.26	147766	3.70
	aug	3999049	410448	10.26	148270	3.71
	sep	4007452	410798	10.25	147335	3.68
	oct	4015565	410464	10.22	146667	3.65
	nov	4014915	407292	10.14	144820	3.61
	dec	4015418	408267	10.17	144360	3.60
2017	jan	4079244	415421	10.18	146460	3.59
	feb	4085373	410861	10.06	143055	3.50
	mar	4088409	414796	10.15	145203	3.55
	apr	4087564	403366	9.87	139339	3.41
	may	4082806	402015	9.85	138947	3.40
	jun	4094037	400154	9.77	137634	3.36
	jul	4119019	396588	9.63	134816	3.27
	aug	4127658	397695	9.63	134743	3.26
	sep	4136603	394258	9.53	131722	3.18
	oct	4143479	395142	9.54	131401	3.17
	nov	4146048	391999	9.45	128729	3.10
	dec	4146225	387520	9.35	125694	3.03

Supplementary Table S3. Monthly denominator, numerator, and prevalence of benzodiazepine use and benzodiazepine-opioid co-prescribing in a commercial population, 2013 to 2017

Year	Month	Denominator	BZD		BZD-opioid	
			Numerator	Prevalence (%)	Numerator	Prevalence (%)
2013	jan	5005168	264430	5.28	91779	1.83
	feb	4993705	310686	6.22	107453	2.15
	mar	4990843	330135	6.61	114809	2.30
	apr	4996512	329278	6.59	113538	2.27
	may	4998913	323637	6.47	112060	2.24
	jun	4999533	321635	6.43	110609	2.21
	jul	4995280	329236	6.59	113403	2.27
	aug	4988273	334267	6.70	115497	2.32
	sep	4978830	333299	6.69	114447	2.30
	oct	4972313	341017	6.86	118352	2.38
	nov	4961877	336926	6.79	115834	2.33
	dec	4957681	339770	6.85	117115	2.36
2014	jan	4785173	321132	6.71	111157	2.32
	feb	4863907	328144	6.75	112424	2.31
	mar	4831156	337096	6.98	116246	2.41
	apr	4816244	338266	7.02	116537	2.42
	may	4791897	338198	7.06	117448	2.45
	jun	4775814	334491	7.00	115664	2.42
	jul	4762167	336612	7.07	116634	2.45
	aug	4732491	332852	7.03	114633	2.42
	sep	4716184	331228	7.02	112933	2.39
	oct	4694055	333822	7.11	113513	2.42
	nov	4681873	324089	6.92	107330	2.29
	dec	4677048	327515	7.00	109212	2.34
2015	jan	5294290	349205	6.60	114742	2.17
	feb	5296817	351057	6.63	114664	2.16
	mar	5324446	360978	6.78	119354	2.24
	apr	5309505	362222	6.82	120101	2.26
	may	5296808	358429	6.77	118876	2.24
	jun	5283477	356622	6.75	118603	2.24
	jul	5272556	359878	6.83	120793	2.29
	aug	5268850	357180	6.78	119337	2.26
	sep	5264546	358156	6.80	119373	2.27
	oct	5256250	361241	6.87	120829	2.30
	nov	5245260	354950	6.77	116903	2.23
	dec	5249639	358916	6.84	119636	2.28
2016	jan	6199239	409831	6.61	141051	2.28
	feb	6187356	422864	6.83	146750	2.37
	mar	6184461	430644	6.96	149973	2.43
	apr	6183861	426269	6.89	147643	2.39
	may	6175705	422112	6.84	145611	2.36
	jun	6175595	421987	6.83	144740	2.34
	jul	6205303	419998	6.77	143776	2.32
	aug	6202267	422495	6.81	145198	2.34
	sep	6198508	422617	6.82	144670	2.33

	oct	6204733	422242	6.81	144212	2.32
	nov	6203647	421273	6.79	142465	2.30
	dec	6225693	423394	6.80	143581	2.31
2017	jan	6966315	454143	6.52	150173	2.16
	feb	6955011	463996	6.67	152264	2.19
	mar	6960146	476401	6.84	157521	2.26
	apr	6967596	467107	6.70	152486	2.19
	may	6966715	468606	6.73	152947	2.20
	jun	6966468	467210	6.71	151489	2.17
	jul	6963951	461441	6.63	148685	2.14
	aug	6963681	462412	6.64	148765	2.14
	sep	6857684	452038	6.59	143832	2.10
	oct	6853558	452225	6.60	143244	2.09
	nov	6856648	448606	6.54	140815	2.05
	dec	6873603	444845	6.47	138984	2.02

Supplementary Table S4. Monthly denominator, numerator, and prevalence of benzodiazepine use and benzodiazepine-opioid co-prescribing in the VA population, 2013 to 2017

Year	Month	Denominator	BZD		BZD-opioid	
			Numerator	Prevalence (%)	Numerator	Prevalence (%)
2013	jan	4248523	250275	5.89	96637	2.27
	feb	4284152	247751	5.78	95524	2.23
	mar	4272363	247901	5.80	95656	2.24
	apr	4255000	244628	5.75	93992	2.21
	may	4240326	245268	5.78	94584	2.23
	jun	4225278	239957	5.68	91991	2.18
	jul	4212214	239800	5.69	91774	2.18
	aug	4204456	238481	5.67	91579	2.18
	sep	4195400	235576	5.62	89768	2.14
	oct	4203124	237007	5.64	90688	2.16
	nov	4226430	231268	5.47	87828	2.08
	dec	4221705	228465	5.41	86636	2.05
2014	jan	4306977	235726	5.47	90489	2.10
	feb	4296217	231719	5.39	87855	2.04
	mar	4281636	231604	5.41	87589	2.05
	apr	4267695	229606	5.38	86536	2.03
	may	4256161	226726	5.33	85333	2.00
	jun	4246250	222803	5.25	83519	1.97
	jul	4242423	223917	5.28	84101	1.98
	aug	4232865	219341	5.18	81077	1.92
	sep	4223624	216834	5.13	78885	1.87
	oct	4229742	217628	5.15	78408	1.85
	nov	4256949	209265	4.92	72378	1.70
	dec	4252621	207805	4.89	71628	1.68
2015	jan	4345571	213050	4.90	73725	1.70
	feb	4334855	207954	4.80	71273	1.64
	mar	4322720	207068	4.79	70712	1.64
	apr	4309687	206283	4.79	69814	1.62
	may	4296473	200584	4.67	67029	1.56
	jun	4280687	197789	4.62	65733	1.54
	jul	4268976	198195	4.64	65921	1.54
	aug	4258169	193104	4.53	63485	1.49
	sep	4251353	191190	4.50	62489	1.47
	oct	4256004	189738	4.46	61518	1.45
	nov	4275660	184317	4.31	58681	1.37
	dec	4276548	183609	4.29	58464	1.37
2016	jan	4368269	185113	4.24	58261	1.33
	feb	4353977	182407	4.19	56873	1.31
	mar	4340880	182106	4.20	56555	1.30
	apr	4325801	178245	4.12	54513	1.26
	may	4314272	173580	4.02	51842	1.20
	jun	4303602	171536	3.99	50440	1.17
	jul	4292277	167989	3.91	48479	1.13
	aug	4279022	165253	3.86	47025	1.10
	sep	4271990	163453	3.83	45824	1.07

	oct	4272495	159320	3.73	43998	1.03
	nov	4283862	155667	3.63	42055	0.98
	dec	4276345	153950	3.60	40757	0.95
2017	jan	4353283	154294	3.54	40316	0.93
	feb	4347173	151429	3.48	38771	0.89
	mar	4333022	151797	3.50	38650	0.89
	apr	4317775	146548	3.39	36033	0.83
	may	4300043	143816	3.34	34619	0.81
	jun	4288165	141863	3.31	33587	0.78
	jul	4277205	139102	3.25	32293	0.76
	aug	4266773	136962	3.21	31393	0.74
	sep	4259758	134380	3.15	30287	0.71
	oct	4259686	133674	3.14	29592	0.69
	nov	4275401	130836	3.06	28342	0.66
	dec	4270459	127384	2.98	27004	0.63

Supplementary Table S5. Trends in monthly likelihood of benzodiazepine-opioid co-prescribing requiring ≥ 1 day of overlap for adults ≥ 55 in Medicare, commercial, and VA populations from 2013 to 2017

Characteristic	Benzodiazepine-Opioid Co-Prescribing ^a	
	Estimate (95% CI)	p-value
Sex		
Female	ref	
Male	-0.51 (-0.72, -0.30)	<0.001
Age		
55-64	ref	
65-74	-0.60 (-0.90, -0.30)	<0.001
75-84	-0.90 (-1.20, -0.60)	<0.001
≥ 85	-1.13 (-1.43, -0.83)	<0.001
Time (months)	-0.004 (-0.004, -0.004)	<0.001
Commercial x time	0.003 (0.003, 0.003)	<0.001
VA x time	-0.02 (-0.02, -0.02)	<0.001
Commercial	-0.71 (-0.97, -0.45)	<0.001
VA	-0.65 (-0.91, -0.39)	<0.001

ref: reference

^a Results from generalized linear mixed models with Poisson distribution for the number of people prescribed benzodiazepines (or co-prescribed a benzodiazepine and opioid) each month from April 2013 to December 2017 to compare systems (Medicare [ref], commercial, and VA) over time, adjusting for age and gender.

Supplementary Table S6. Annual rates and standardized ratios of benzodiazepine-opioid co-prescribing requiring ≥1 day of overlap in Medicare, commercial, and VA populations in 2017

Characteristics	Benzodiazepine-opioid co-prescribing				
	Medicare	Commercial		VA	
	Rate ^a (per 100 person-yr)	Rate ^a (per 100 person-yr)	Standardized ratio ^b (95% CI) ^c	Rate ^a (per 100 person-yr)	Standardized ratio ^b (95% CI) ^c
Overall	7.6	5.1	0.64 (0.64, 0.65)	2.1	0.35 (0.35, 0.35)
Sex					
Male	5.6	3.7	0.64 (0.64, 0.65)	2.0	0.36 (0.36, 0.36)
Female	9.0	6.2	0.64 (0.64, 0.65)	3.3	0.27 (0.27, 0.28)
Age (years)					
55-64	18.4	5.7	0.54 (0.54, 0.54)	2.8	0.26 (0.26, 0.27)
65-74	6.5	5.0	0.74 (0.74, 0.75)	2.3	0.45 (0.45, 0.46)
75-84	6.3	4.5	0.73 (0.73, 0.74)	1.2	0.37 (0.37, 0.38)
≥85	6.8	4.4	0.67 (0.66, 0.68)	1.1	0.37 (0.36, 0.38)
Clinical conditions					
Depression	22.5	15.1	0.72 (0.72, 0.73)	5.7	0.38 (0.38, 0.39)
Anxiety d/o	31.2	20.7	0.72 (0.72, 0.73)	8.7	0.40 (0.39, 0.40)
PTSD	32.2	23.9	0.75 (0.73, 0.77)	6.1	0.52 (0.51, 0.53)
Alcohol-related d/o	16.3	10.7	0.78 (0.76, 0.79)	3.1	0.30 (0.30, 0.31)
Non-alcohol substance-related d/o	36.7	29.4	0.86 (0.85, 0.88)	4.8	0.26 (0.26, 0.27)
Dementia	13.0	8.3	0.68 (0.67, 0.69)	2.9	0.41 (0.40, 0.43)
Insomnia	24.9	16.3	0.73 (0.73, 0.74)	6.0	0.38 (0.37, 0.39)
Chronic pain	12.9	7.4	0.66 (0.66, 0.66)	3.4	0.37 (0.37, 0.38)
Elixhauser score					
0	3.5	2.0	0.57 (0.56, 0.57)	0.7	0.26 (0.26, 0.27)
1	6.3	3.3	0.52 (0.51, 0.52)	1.4	0.29 (0.29, 0.30)
2	7.8	4.5	0.58 (0.57, 0.58)	1.8	0.32 (0.31, 0.32)
3	9.4	5.7	0.63 (0.62, 0.63)	2.4	0.35 (0.34, 0.35)
4+	14.1	9.2	0.74 (0.73, 0.74)	4.0	0.42 (0.42, 0.43)
Prescribed opioid	18.6	15.6	0.67 (0.67, 0.67)	7.2	0.38 (0.37, 0.38)

CI: confidence interval; d/o: disorder.

^a 100 x number of persons with any benzodiazepine (or benzodiazepine and opioid) use in 2017 / total person-years, either overall or by stratum, where person-year is 1 if an eligible individual is alive throughout the year or a fraction (number of days to death or hospice care/365) if died or entered hospice during 2017

^b (observed number of persons with benzodiazepine prescription in 2017 in commercial or VA) / (expected number of persons with benzodiazepine prescription in 2017, predicted using Poisson multivariable regression model from Medicare population including all table row characteristics)

^c 95% Confidence Interval (CI) = rate ± (1.96 x [√observed]/expected)¹

Supplementary Table S7. Annual rates and standardized ratios of benzodiazepine prescribing and benzodiazepine-opioid co-prescribing, limited to adults ≥65 in Medicare, Commercial, and VA populations in 2017

Characteristics	Benzodiazepine prescribing					Benzodiazepine-opioid co-prescribing				
	Medicare	Commercial		VA		Medicare	Commercial		VA	
	Rate ^a (per 100 person-yr)	Rate ^a (per 100 person-yr)	Standardized ratio ^b (95% CI) ^c	Rate ^a (per 100 person-yr)	Standardized ratio ^b (95% CI) ^c	Rate ^a (per 100 person-yr)	Rate ^a (Rx per 100 person-yr)	Standardized ratio ^b (95% CI) ^c	Rate ^a (per 100 person-yr)	Standardized ratio ^b (95% CI) ^c
Overall	16.4	12.3	0.69 (0.69, 0.69)	5.9	0.45 (0.45, 0.45)	7.0	5.1	0.72 (0.71, 0.72)	2.0	0.41 (0.40, 0.41)
Sex										
Male	12.0	8.9	0.70 (0.69, 0.70)	5.9	0.45 (0.45, 0.45)	5.0	3.7	0.73 (0.73, 0.74)	1.9	0.41 (0.40, 0.41)
Female	19.4	14.9	0.69 (0.69, 0.69)	8.2	0.39 (0.38, 0.40)	8.3	6.2	0.71 (0.70, 0.71)	2.9	0.35 (0.34, 0.37)
Age (years)										
65-74	15.9	12.3	0.70 (0.70, 0.70)	6.9	0.48 (0.48, 0.49)	7.0	5.4	0.73 (0.72, 0.73)	2.4	0.42 (0.42, 0.43)
75-84	16.5	12.2	0.70 (0.69, 0.70)	4.3	0.38 (0.38, 0.38)	6.8	4.9	0.72 (0.71, 0.73)	1.3	0.36 (0.35, 0.37)
≥85	18.2	12.1	0.63 (0.63, 0.64)	4.0	0.36 (0.36, 0.37)	7.2	4.7	0.65 (0.65, 0.66)	1.2	0.36 (0.35, 0.37)
Clinical conditions										
Depression	39.5	27.9	0.74 (0.74, 0.75)	15.9	0.58 (0.58, 0.59)	20.8	14.1	0.76 (0.75, 0.77)	5.7	0.46 (0.45, 0.47)
Anxiety d/o	57.0	42.9	0.78 (0.78, 0.79)	27.5	0.63 (0.62, 0.64)	29.0	19.9	0.78 (0.77, 0.78)	8.7	0.47 (0.46, 0.48)
PTSD	49.0	35.1	0.72 (0.70, 0.74)	18.0	0.75 (0.74, 0.75)	27.0	19.2	0.76 (0.73, 0.79)	6.1	0.56 (0.55, 0.57)
Alcohol-related d/o	27.2	18.5	0.78 (0.76, 0.79)	9.0	0.46 (0.45, 0.47)	14.2	9.2	0.81 (0.78, 0.83)	3.3	0.40 (0.38, 0.41)
Non-alcohol substance-related d/o	43.9	37.6	0.92 (0.91, 0.93)	12.4	0.45 (0.44, 0.46)	35.8	27.0	0.85 (0.84, 0.87)	5.7	0.33 (0.31, 0.34)
Dementia	31.0	20.2	0.65 (0.65, 0.66)	8.9	0.46 (0.45, 0.47)	13.4	8.5	0.67 (0.66, 0.68)	3.0	0.43 (0.42, 0.45)
Insomnia	43.7	32.0	0.79 (0.78, 0.79)	17.8	0.61 (0.60, 0.62)	23.3	15.6	0.78 (0.77, 0.79)	6.1	0.46 (0.45, 0.47)
Chronic pain	22.0	14.8	0.69 (0.69, 0.70)	8.0	0.49 (0.49, 0.49)	11.6	7.0	0.72 (0.71, 0.72)	3.3	0.45 (0.44, 0.45)
Elixhauser score										
0	10.0	7.2	0.74 (0.74, 0.75)	2.8	0.35 (0.35, 0.36)	3.2	2.2	0.81 (0.80, 0.82)	0.7	0.31 (0.30, 0.32)
1	15.7	9.5	0.61 (0.60, 0.61)	4.7	0.39 (0.38, 0.39)	5.7	3.1	0.62 (0.61, 0.62)	1.2	0.34 (0.33, 0.35)
2	17.4	11.3	0.65 (0.64, 0.65)	5.5	0.42 (0.41, 0.42)	7.1	4.1	0.65 (0.64, 0.66)	1.6	0.36 (0.35, 0.37)
3	19.4	12.8	0.67 (0.67, 0.68)	6.7	0.45 (0.45, 0.46)	8.7	5.2	0.69 (0.68, 0.69)	2.1	0.39 (0.38, 0.40)
4+	24.7	16.7	0.73 (0.73, 0.73)	9.3	0.54 (0.53, 0.54)	13.2	8.3	0.75 (0.75, 0.76)	3.9	0.48 (0.48, 0.49)
Prescribed opioid	25.3	22.5	0.78 (0.78, 0.78)	11.8	0.54 (0.53, 0.54)	17.1	15.1	0.75 (0.74, 0.75)	7.4	0.47 (0.46, 0.47)

: Veterans Affairs; CI: confidence interval; d/o: disorder.

^a100 x number of persons with any benzodiazepine (or benzodiazepine and opioid) use in 2017 / total person-years, either overall or by stratum, where person-year is 1 if an eligible individual is alive throughout the year or a fraction (number of days to death or hospice care/365) if died or entered hospice during 2017

^b(observed number of persons with benzodiazepine prescription in 2017 in Optum or VA) / (expected number of persons with benzodiazepine prescription in 2017, predicted using Poisson multivariable regression model from Medicare population including all table row characteristics)

^c 95% Confidence Interval (CI) = rate ± (1.96 x [√observed]/expected)