

This supplementary material has been provided by the authors to provide readers additional information about their work.

eAppendix A. Supplement for inclusion and exclusion diagnoses

Appendix Table A1: Exclusion Diagnoses for Opioid-Antidepressant Analyses

ICD-10 Code	ICD-9 Code	Description	Notes
F20.*	295.*	Schizophrenia	http://www.icd9data.com/2012/Volume1/290-319/295-299/295/default.htm
F23.*	298.3/298.4/298.8	Brief Psychotic Disorder	https://www.icd10data.com/Convert/F23
F24.*	297.3	Shared Psychotic Disorder	https://www.icd10data.com/Convert/F24
F25.*	295.7	Schizoaffective Disorders	https://www.icd10data.com/Convert/F25.0
F28.*	298.9	Other psychotic disorder not due to a substance or known physiological condition	https://www.icd10data.com/Convert/F28
F29.*	298.9	Unspecified psychosis not due to a substance or known physiological condition	https://www.icd10data.com/Convert/F29
F30.*	296.06	Manic episode	https://www.icd10data.com/Convert/F30.4
F31.*	296.05	Bipolar disorder	https://www.icd10data.com/Convert/F30.3
F34.0	301.13	Cyclothymic disorder	https://www.icd10data.com/Convert/F34.0

Notes: * indicates all subcodes after the decimal point should also be excluded from the denominator. Individuals were excluded if they had at least one of these diagnoses recorded within the 6 months before the start of the OA episode, or the 12 months following the start of the OA episode.

Appendix Table A2: Inclusion Depression Diagnoses for Opioid-Antidepressant Analyses

ICD-10 Code	ICD-9 Code	Description	Notes
F32.0/F32.1/F32.2/F32.3/F32.4/F32.5/F32.9	296.2*	MDD single episode (and all subcodes)	ICD9-ICD10 crosswalk from NBER: https://data.nber.org/data/icd9-icd-10-cm-and-pcs-crosswalk-general-equivalence-mapping.html
F33.0/F33.1/F33.2/F33.3/F33.4/F33.9	296.3*	MDD recurrent episode (and all subcodes)	
F34.1	300.4	Dysthymic disorder	

Notes: * indicates all subcodes after the decimal point should also be included in the denominator. Individuals with an OA episode were eligible for inclusion in our sample if they had an ED or inpatient visit in the 6 months prior to the start of the OA episode with a depression diagnosis in any position on a claim.

eAppendix B. Supplement for ICD-9 and ICD-10 codes for adverse events

Appendix Table B1: ICD-9 and ICD-10 of the adverse events

Category	ICD-9 Groups Included	ICD-10 Groups Included
Self-harm not related to poisoning	E9506, E9507, E9508, E9509, E951.*, E952.*, E953.*, E954.*, E955.*, E956.*, E957.*, E958.*	T14.91, T14.91*, X71.*, X72.*, X73.*, X74.*, X75.*, X76.*, X77.*, X78.*, X79.*, X80.*, X81.*, X82.*, X83.*
Opioid poisonings	9650, 96500, 96501, 96502, 96509, E9500, E9800, E8500, E8501, E8502	<i>Intentional opioid poisonings:</i> T40.0X2*, T40.1X2*, T40.2X2*, T40.3X2*, T40.4X2* <i>Unintentional opioid poisonings:</i> T40.0X1*, T40.1X1*, T40.2X1*, T40.3X1*, T40.4X1* <i>Opioid poisonings unclear intent:</i> T40.0X4*, T40.1X4*, T40.2X4*, T40.3X4*, T40.4X4*
Non-opioid controlled substances poisonings	9694, 9670, 97081, E9501, E9801, E851, E8532	<i>Intentional non-opioid controlled substances poisonings:</i> T40.5X2*, T40.60X2*, T40.69X2*, T40.7X2*, T40.8X2*, T40.90X2*, T40.99X2*, T42.3X2*, T42.4X2*, T43.642* <i>Unintentional non-opioid controlled substances poisonings:</i> T40.5X1*, T40.60X1*, T40.69X1*, T40.7X1*, T40.8X1*, T40.90X1*, T40.99X1*, T42.3X1*, T42.4X1*, T43.641* <i>Non-opioid controlled substances poisonings unclear intent:</i> T40.5X4*, T40.60X4*, T40.69X4*, T40.7X4*, T40.8X4*, T40.90X4*, T40.99X4*, T42.3X4*, T42.4X4*, T43.644*
Other poisonings	960.*, 961.*, 962.*, 963.*, 964.*, 9651, 9654, 9655, 9656, 96561, 96569, 9657, 9658, 9659, 966.*, 9671, 9672, 9673, 9674, 9675, 9676, 9678, 9679, 968.*, 9690, 96900, 96901, 96902, 96903, 96904, 96905, 96909, 9691, 9692, 9693, 9695, 9696, 9697, 96970, 96971, 96972, 96973, 96979, 9698, 9699, 9700, 9701, 9708, 97089, 9709, 971.*, 972.*, 973.*, 974.*, 975.*, 976.*, 977.*, 978.*, 979.*, E9502, E9503, E9504, E9505, E9802, E9803, E9804, E9805, E9806, E9807, E9808, E9809, E981, E9810, E9811, E9818, E982, E9820, E9821, E9828, E9829, E8503, E8504, E8505, E8506, E8507, E8508, E8509, E852, E8520, E8521, E8522, E8523, E8524, E8525, E8528, E8529, E853, E8530, E8531, E8538, E8539, E854, E8540, E8541, E8542, E8543, E8548,	<i>Intentional other poisonings:</i> T36.0X2*, T36.1X2*, T36.2X2*, T36.3X2*, T36.4X2*, T36.5X2*, T36.6X2*, T36.7X2*, T36.8X2*, T36.92*, T37.0X2*, T37.1X2*, T37.2X2*, T37.3X2*, T37.4X2*, T37.5X2*, T37.8X2*, T37.92*, T38.0X2*, T38.1X2*, T38.2X2*, T38.3X2*, T38.4X2*, T38.5X2*, T38.6X2*, T38.7X2*, T38.802*, T38.812*, T38.892*, T38.902*, T38.992*, T39.012*, T39.092*, T39.1X2*, T39.2X2*, T39.312*, T39.392*, T39.4X2*, T39.8X2*, T39.92*, T41.0X2*, T41.1X2*, T41.202*, T41.292*, T41.3X2*, T41.42*, T41.5X2*, T42.0X2*, T42.1X2*, T42.2X2*, T42.5X2*, T42.6X2*, T42.72*, T42.8X2*, T43.012*, T43.022*, T43.1X2*, T43.202*, T43.212*, T43.222*, T43.292*, T43.3X2*, T43.4X2*, T43.502*, T43.592*, T43.602*, T43.612*, T43.622*, T43.632*, T43.692*, T43.8X2*, T43.92*, T44.0X2*, T44.1X2*, T44.2X2*, T44.3X2*, T44.4X2*, T44.5X2*, T44.6X2*, T44.7X2*, T44.8X2*, T44.902*, T44.992*, T45.0X2*, T45.1X2*, T45.2X2*, T45.3X2*, T45.4X2*, T45.512*, T45.522*, T45.602*, T45.612*, T45.622*, T45.692*, T45.7X2*, T45.8X2*, T45.92*, T46.0X2*, T46.1X2*, T46.2X2*, T46.3X2*, T46.4X2*, T46.5X2*, T46.6X2*, T46.7X2*, T46.8X2*, T46.902*, T46.992*, T47.0X2*, T47.1X2*, T47.2X2*, T47.3X2*, T47.4X2*, T47.5X2*, T47.6X2*, T47.7X2*, T47.8X2*, T47.92*, T48.0X2*, T48.1X2*, T48.202*, T48.292*, T48.3X2*, T48.4X2*, T48.5X2*, T48.6X2*, T48.902*, T48.992*, T49.0X2*, T49.1X2*, T49.2X2*, T49.3X2*, T49.4X2*, T49.5X2*, T49.6X2*, T49.7X2*, T49.8X2*, T49.92*, T50.0X2*, T50.1X2*, T50.2X2*, T50.3X2*, T50.4X2*, T50.5X2*, T50.6X2*, T50.7X2*, T50.8X2*, T50.A12*, T50.A22*, T50.A92*, T50.B12*, T50.B92*, T50.Z12*, T50.Z92*, T50.902*, T50.912*, T50.992*

E855, E8550, E8551, E8552, E8553,
E8554, E8555, E8556, E8558, E8559,
E856, E857, E858, E8580, E8581, E8582,
E8583, E8584, E8585, E8586, E8587,
E8588, E8589

Unintentional other poisonings: T36.0X1*, T36.1X1*, T36.2X1*, T36.3X1*, T36.4X1*, T36.5X1*,
T36.6X1*, T36.7X1*, T36.8X1*, T36.91*, T37.0X1*, T37.1X1*, T37.2X1*, T37.3X1*, T37.4X1*,
T37.5X1*, T37.8X1*, T37.91*, T38.0X1*, T38.1X1*, T38.2X1*, T38.3X1*, T38.4X1*, T38.5X1*,
T38.6X1*, T38.7X1*, T38.801*, T38.811*, T38.891*, T38.901*, T38.991*, T39.011*, T39.091*, T39.1X1*,
T39.2X1*, T39.311*, T39.391*, T39.4X1*, T39.8X1*, T39.91*, T41.0X1*, T41.1X1*, T41.201*, T41.291*,
T41.3X1*, T41.41*, T41.5X1*, T42.0X1*, T42.1X1*, T42.2X1*, T42.5X1*, T42.6X1*, T42.71*, T42.8X1*,
T43.011*, T43.021*, T43.1X1*, T43.201*, T43.211*, T43.221*, T43.291*, T43.3X1*, T43.4X1*, T43.501*,
T43.591*, T43.601*, T43.611*, T43.621*, T43.631*, T43.691*, T43.8X1*, T43.91*, T44.0X1*, T44.1X1*,
T44.2X1*, T44.3X1*, T44.4X1*, T44.5X1*, T44.6X1*, T44.7X1*, T44.8X1*, T44.901*, T44.991*,
T45.0X1*, T45.1X1*, T45.2X1*, T45.3X1*, T45.4X1*, T45.511*, T45.521*, T45.601*, T45.611*, T45.621*,
T45.691*, T45.7X1*, T45.8X1*, T45.91*, T46.0X1*, T46.1X1*, T46.2X1*, T46.3X1*, T46.4X1*, T46.5X1*,
T46.6X1*, T46.7X1*, T46.8X1*, T46.901*, T46.991*, T47.0X1*, T47.1X1*, T47.2X1*, T47.3X1*,
T47.4X1*, T47.5X1*, T47.6X1*, T47.7X1*, T47.8X1*, T47.91*, T48.0X1*, T48.1X1*, T48.201*, T48.291*,
T48.3X1*, T48.4X1*, T48.5X1*, T48.6X1*, T48.901*, T48.991*, T49.0X1*, T49.1X1*, T49.2X1*,
T49.3X1*, T49.4X1*, T49.5X1*, T49.6X1*, T49.7X1*, T49.8X1*, T49.91*, T50.0X1*, T50.1X1*,
T50.2X1*, T50.3X1*, T50.4X1*, T50.5X1*, T50.6X1*, T50.7X1*, T50.8X1*, T50.A11*, T50.A21*,
T50.A91*, T50.B11*, T50.B91*, T50.Z11*, T50.Z91*, T50.901*, T50.911*, T50.991*

Other poisonings unclear intent: T36.0X4*, T36.1X4*, T36.2X4*, T36.3X4*, T36.4X4*, T36.5X4*,
T36.6X4*, T36.7X4*, T36.8X4*, T36.94*, T37.0X4*, T37.1X4*, T37.2X4*, T37.3X4*, T37.4X4*,
T37.5X4*, T37.8X4*, T37.94*, T38.0X4*, T38.1X4*, T38.2X4*, T38.3X4*, T38.4X4*, T38.5X4*,
T38.6X4*, T38.7X4*, T38.804*, T38.814*, T38.894*, T38.904*, T38.994*, T39.014*, T39.094*, T39.1X4*,
T39.2X4*, T39.314*, T39.394*, T39.4X4*, T39.8X4*, T39.94*, T41.0X4*, T41.1X4*, T41.204*, T41.294*,
T41.3X4*, T41.44*, T41.5X4*, T42.0X4*, T42.1X4*, T42.2X4*, T42.5X4*, T42.6X4*, T42.74*, T42.8X4*,
T43.014*, T43.024*, T43.1X4*, T43.204*, T43.214*, T43.224*, T43.294*, T43.3X4*, T43.4X4*, T43.504*,
T43.594*, T43.604*, T43.614*, T43.624*, T43.634*, T43.694*, T43.8X4*, T43.94*, T44.0X4*, T44.1X4*,
T44.2X4*, T44.3X4*, T44.4X4*, T44.5X4*, T44.6X4*, T44.7X4*, T44.8X4*, T44.904*, T44.994*,
T45.0X4*, T45.1X4*, T45.2X4*, T45.3X4*, T45.4X4*, T45.514*, T45.524*, T45.604*, T45.614*, T45.624*,
T45.694*, T45.7X4*, T45.8X4*, T45.94*, T46.0X4*, T46.1X4*, T46.2X4*, T46.3X4*, T46.4X4*, T46.5X4*,
T46.6X4*, T46.7X4*, T46.8X4*, T46.904*, T46.994*, T47.0X4*, T47.1X4*, T47.2X4*, T47.3X4*,
T47.4X4*, T47.5X4*, T47.6X4*, T47.7X4*, T47.8X4*, T47.94*, T48.0X4*, T48.1X4*, T48.204*, T48.294*,
T48.3X4*, T48.4X4*, T48.5X4*, T48.6X4*, T48.904*, T48.994*, T49.0X4*, T49.1X4*, T49.2X4*,
T49.3X4*, T49.4X4*, T49.5X4*, T49.6X4*, T49.7X4*, T49.8X4*, T49.94*, T50.0X4*, T50.1X4*,
T50.2X4*, T50.3X4*, T50.4X4*, T50.5X4*, T50.6X4*, T50.7X4*, T50.8X4*, T50.A14*, T50.A24*,
T50.A94*, T50.B14*, T50.B94*, T50.Z14*, T50.Z94*, T50.904*, T50.914*, T50.994*

Appendix Table B2: Frequency of Adverse Events

Period	Any adverse event	Opioid poisonings	Non-opioid controlled substances poisonings	Other poisonings	Self-harm
2007-2017	45,756	4,451	5,610	32,555	3,189
Percent	100.0	9.7	12.3	71.1	7.0

Notes: The data come from Optum's de-identified Clinformatics® Data Mart Database 2007 to 2017. This table reported any adverse encounters of adults prescribed opioid analgesics during 2007-2017. The top 5 ICD-9/ICD-10 for each category were provided in the Appendix Table B3.

Appendix Table B3: Top ICD codes for each adverse event category

ICD-9 (prior to October 2015)	Optum Description	Frequency	Cumulative percent	ICD-10 (post October 2015)	Optum Description	Frequency	Cumulative percent
Opioid poisonings							
965.09	POISN OPIATES&RELATED NARCOTICS OTH	1220	40.8	T40.2X1A	POISON OTH OPIOIDS ACC INITIAL ENC	524	29.8
965.00	POISONING BY OPIUM , UNSPECIFIED	641	62.2	T40.1X1A	POISON HEROIN ACCIDENTAL INIT ENC	302	47.0
E950.0	SUI&SLF-PSN-ANALGES- ANTIPYRET	387	75.2	T40.2X2A	POISN OTH OPIOIDS SLF-HARM INIT ENC	269	62.3
965.01	POISONING BY HEROIN	297	85.1	T40.4X1A	PSN OTH SYNTH NARCOTIC ACC INIT ENC	157	71.3
E980.0	PSN-ANALGES- ANTIPYRET-ANTIRHM- UNDET	191	91.5	T40.2X4A	POISN OTH OPIOIDS UNDET INITIAL ENC	89	76.3
Non-opioid controlled substances poisonings							
969.4	POISN BENZODIAZEPINE- BASED TRANQ	3321	88.8	T42.4X2A	POISN BENZODIAZEPINES SLF- HARM INIT	764	37.2
967.0	POISONING BY BARBITURATES	152	92.9	T42.4X1A	POISON BENZODIAZEPINES ACC INIT ENC	696	71.0
970.81	POISONING BY COCAINE	111	95.8	T42.4X4A	POISN BENZODIAZEPINES UNDET INITIAL	168	79.2
E853.2	ACC PSN BENZODIAZEPINE-BASED TRANQ	105	98.6	T42.4X1D	POISON BENZODIAZEPINES ACC SUB ENC	68	82.5
E980.1	PSN BARBITURATS UNDETRM ACC/PURPOSE	24	99.3	T42.4X2D	POISN BENZODIAZEPINES SELF-HARM SUB	65	85.7
Other poisonings							

977.9	POISN UNSPEC RX/MEDICINAL SUBSTANCE	8343	38.2	T50.901A	POISN UNS RX MEDS BIO SUBS ACC INIT	1887	16.1
965.4	POISONING AROMATIC ANALGESICS NEC	1269	44.0	T50.902A	PSN UNS RX MED BIO SUBS SF-HRM INIT	1499	28.8
977.8	POISN OTH SPEC RX&MEDICINAL SBSTNC	978	48.5	T50.904A	PSN UNS RX MEDS BIO SUBS UNDET INIT	974	37.1
E950.3	SUI&SLF-INFLCT PSN- TRANQ&PSYCHOTROP	743	51.9	T45.511A	POISN ANTICOAG ACCIDENT INITIAL ENC	482	41.2
967.8	POISONING OTHER SEDATIVES&HYPNOTICS	636	54.8	T39.1X2A	PSN 4-AMINOPHENOL DER SLF-HARM INIT	344	44.2
Self-harm							
E956	SUIE&SLF-INJURY- CUT&PIERC INSTRUM	329	26.7	T14.91	SUICIDE ATTEMPT	1452	68.6
E958.9	SUICIDE&SLF-INFLCTED INJR UNS MEANS	291	50.4	T14.91XA	SUICIDE ATTEMPT INITIAL ENCOUNTER	184	77.3
E950.9	SUI&SLF-POISN-UNS SOLID&LQD SBSTNC	142	62.0	X83.8XXA	INTENTIONAL SH OTH SPECI MEANS INIT	95	81.8
E955.1	SUICIDE&SELF-INFLICT INJURY SHOTGUN	116	71.4	X73.0XXA	SELF-HARM SHOTGUN D/C INITIAL	61	84.7
E955.0	SUI&SELF-INFLICT INJURY BY HANDGUN	85	78.3	X78.9XXA	INTENTIONL SH UNS SHARP OBJECT INIT	61	87.6

Notes: The data come from Optum's de-identified Clinformatics® Data Mart Database 2007 to 2017. This table reported the adverse encounters during 2007-2017 of adults prescribed opioid analgesics with a prior ED/inpatient visit for depression.