

Data supplement for Nelson and Spyker, Morbidity and Mortality Associated With Medications Used in the Treatment of Depression: An Analysis of Cases Reported to U.S. Poison Control Centers, 2000–2014. Am J Psychiatry (doi: 10.1176/appi.ajp.2016.16050523)

Supplemental Materials

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Supplemental Material 1 – Details of Medication Extraction

Supplemental Material 1 describes the extraction and translation of the NPDS encounter data to the final 59 individual drugs carried out in this study

Generic Codes Extracted (N=50)

<u>Generic Code Name</u>	<u>Generic Code</u>
Amitriptyline	66731
Amoxapine.....	66732
Antidepressants: Type Unknown to Consumer	77732
Atypical Antipsychotics	201122
Benzodiazepines	7000
Bupropion	310019
Buspirone.....	201123
Carbamazepine	249000
Citalopram	310009
Clomipramine	310003
Desipramine.....	66733
Doxepin	66734
Duloxetine	310017
Escitalopram	310010
Fluoxetine	310011
Fluvoxamine	310012
Gabapentin.....	201172
Imipramine.....	66735
Isocarboxazid.....	310005
Lamotrigine	201173

Lithium	101000
Loxapine	310002
Maprotiline	66736
Mirtazapine	310001
Nefazodone	310015
Nortriptyline	66737
Other Types of Antidepressant	77731
Other Types of Gamma Aminobutyric Acid Anticonvulsant	201178
Other Types of Monoamine Oxidase Inhibitor (MAOI)	168000
Other Types of Sedative/Hypnotic/Anti-Anxiety or Anti-Psychotic Drug.....	77941
Other Types of Selective Serotonin Reuptake Inhibitor (SSRI)	66744
Other Types of Serotonin Norepinephrine Reuptake Inhibitor (SNRI)	310018
Other Types of Tricyclic Antidepressant (TCA)	66741
Oxcarbazepine	201176
Paroxetine	310013
Phenelzine.....	310006
Phenothiazines	75000
Protriptyline	66738
Selegiline	310008
Sertraline.....	310014
Topiramate.....	201174
Tranlycypromine	310007
Trazodone	66743
Tricyclic Antidepressants (TCA) Formulated with a Benzodiazepine	66739
Tricyclic Antidepressants (TCA) Formulated with a Phenothiazine.....	66740
Tricyclic Antidepressants (TCA): Type Unknown to Consumer	66742
Trimipramine	310004
Unknown Types of Anticonvulsant (Excluding Barbiturates).....	excluded
Unknown Types of Sedative/Hypnotic/Anti-Anxiety or Anti-Psychotic Drug	77940
Valproic Acid	260000
Venlafaxine.....	310016
Other Types of Anticonvulsant (Excluding Barbiturates)	excluded
Sleep Aids, Over the Counter Only (Excluding Diphenhydramine)	excluded
Zonisamide	excluded

All of the substances extracted from the above 50 Generic Codes included 4517 distinct product (or generic) codes were mapped to the 10 drug groups and 59 drugs listed below

Drug Groups (N=10)

Num	GROUP
1	TCA's
2	MAOIs
3	SSRIs
4	SNRIs
5	Other Antidepressants
6	Atypical Antipsychotics
7	Lithium
8	Anticonvulsants
9	Combination Agents
10	Other Medications

Anticonvulsants, Atypical Antipsychotics, Combination Agents, Lithium, MAOIs, Other Antidepressants, Other Medications, SNRIs, SSRIs, TCAs

Drug List (N=59)

Here's an alphabetical list of the 59 drugs studied.

amitriptyline, amoxapine, aripiprazole, asenapine, benzodiazepines, bupropion, buspirone, carbamazepine, chlorpromazine, citalopram, clomipramine, clozapine, desipramine, desvenlafaxine, doxepin, droperidol, duloxetine, escitalopram, fluoxetine, fluphenazine, fluvoxamine, gabapentin, haloperidol, iloperidone, imipramine, lamotrigine, lithium, loxapine, lurasidone, maprotiline, milnacipran, mirtazapine, molindone, nefazodone, nortriptyline, olanzapine, olanzapine + fluoxetine, oxcarbazepine, paliperidone, paroxetine, perphenazine, perphenazine + amitriptyline, phenelzine, pimozide, pregabalin, protriptyline, quetiapine, risperidone, selegiline, sertraline, thioridazine, thiothixene, tranylcypromine, trazodone, trifluoperazine, valproic acid, venlafaxine, vilazodone, ziprasidone

Supplemental Material 2

Limits on Antidepressant Exposures based on Age and Intent

We considered whether to limit the sample to those over a certain age or based on reason for the exposure, such as suicide. The rationale for the age limit was knowledge that many exposures in children are accidental and our aim in this study was to determine the morbidity and mortality associated with medications used during treatment of depression.

Age. We examined 3 different age thresholds, ≥ 12 years, ≥ 16 yrs, ≥ 20 yrs (Table 2.1). We did not consider a lower age threshold since we were principally interested in the therapeutic use and intentional overdose of these agents. We noted Cochran's Q increased slightly as age decreased from 20 to 16 and 16 to 12, but the increase was larger when children under 12 were included. Similarly the pooled morbidity index changed slightly from 20 to 16 to 12 but with inclusion of children under 12, the index dropped substantially. These data suggested that the group under 12 differed from the larger group and that a threshold of ≥ 12 was most appropriate. This is consistent with the AAPCC annual report which found that the frequency of intentional

exposures in children under 12 years was 1% but jumped to 58% in the 13 to 19 age group. Based on these data we excluded from our sample children under the age of 12.

Table 2.1

Analysis group	Cochran Q*	Pooled Morbidity Index	Between Drug groups variance*	Number of Exposures	Mean of Indices (N=11)**
All Ages	51,278	136	43.7	1,439,710	163
≥ 12 y/o	40,969	171	46.9	1,069,195	197
≥ 16 y/o	39,830	173	50.0	978,079	200
≥ 20 y/o	36,893	175	53.7	844,685	200
Suicide	29,895	222	65.3	569,678	271

*From Forest Plot analysis (Stats Direct)

**Arithmetic mean of Morbidity Indices for 11 drug groups

Reason for the exposure. The reasons for the medication exposure in NPDS includes suspected suicide, and a variety of other possible reasons. We considered whether to include all reasons (in those ≥ 12 years) or limit to suspected suicide. Our considerations were the following.

1. Our aim was to determine the morbidity and mortality of medications used in the treatment of depression.
2. An appreciable number, 1/3 of serious outcomes and 1/4 of fatal outcomes, occur following exposures that are not related to suicide. (see page 8 of the manuscript).
3. A comparison of morbidity indices for 11 drug groups (figures 2.1 and 2.2) suggests that relative morbidity risk between drug groups is minimally affected by limiting reason for the exposure to suicide with the possible exception of lithium and MAOIs. (The 11 medications or drug groups included the 10 drug groups cited above. In this analysis ‘other agents’ and ‘buspirone’ were examined separately).
4. Excluding exposures not related to suicide reduces the total number of exposures by 48%. As we divide these data among the individual drugs, the larger number of exposures for the ≥12 y/o subset with reason = all provides greater statistical power for distinguishing differences between medications. This is especially important for the newer drugs.

Figure 2.1 Forest Plot – 12 y/o and older, exposures for all reasons
 Cochran Q = 40969.351837 (df = 10) P < 0.0001

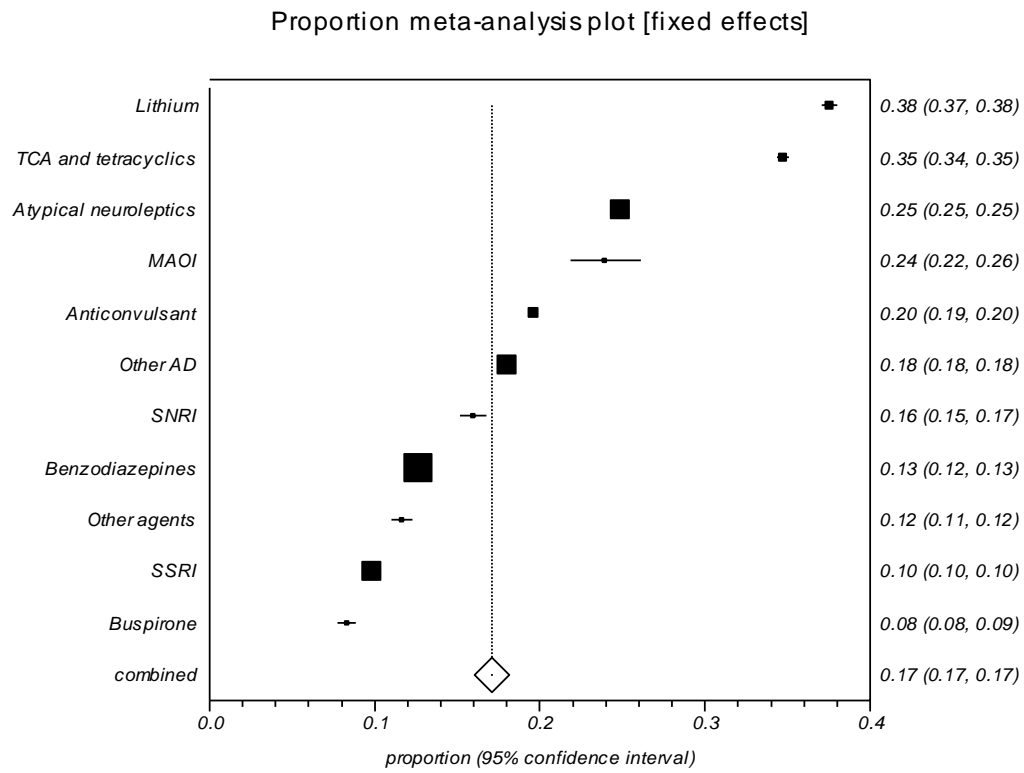
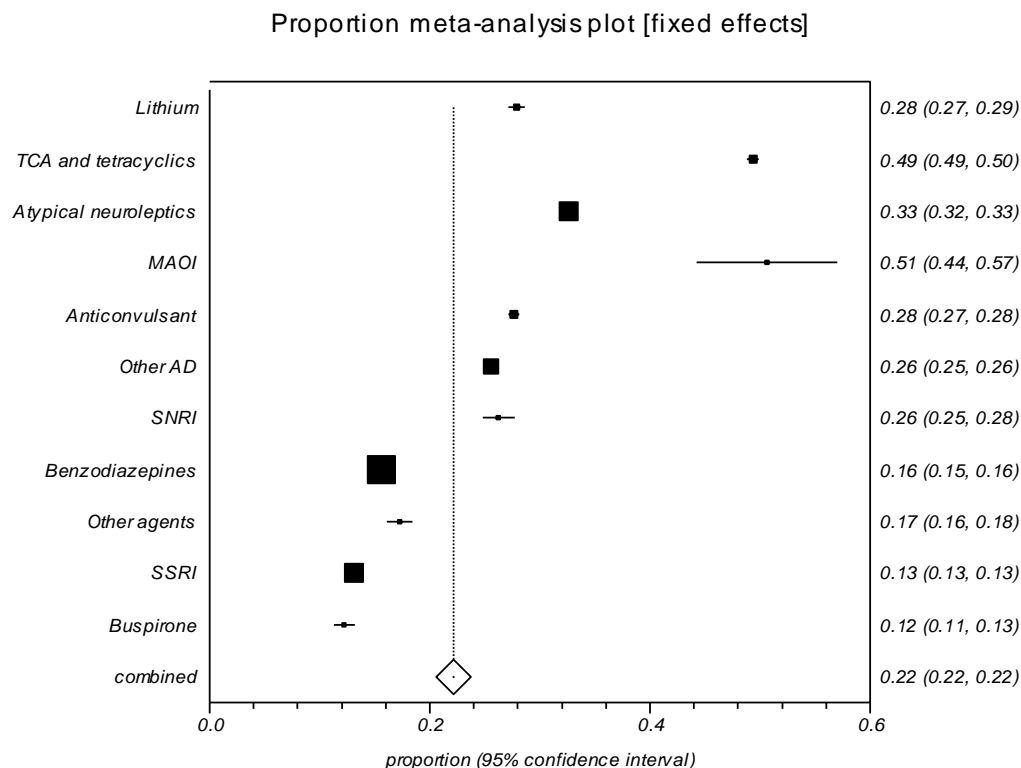


Figure 2.2 Forest Plot – 12 y/o and older, exposures limited to suspect suicide

Cochran Q = 29895.399941 (df = 10) P < 0.0001



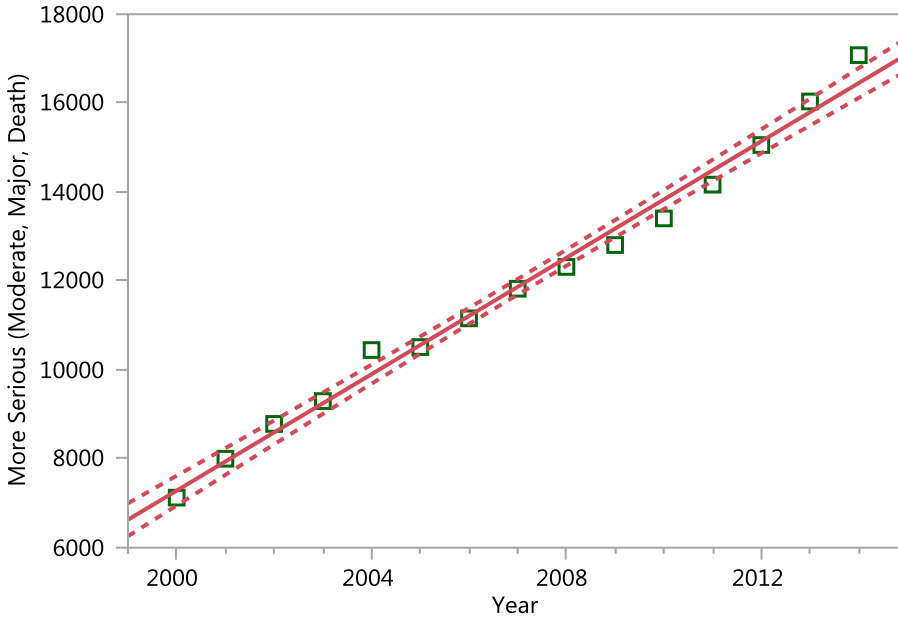
Supplemental Material 3 – Correction for Less Serious Calls

Since approximately 2008, the number of Less Serious Exposures per year reported to US poison centers has decreased despite a consistent increase in the number of More Serious Exposures (Outcome = Major, Moderate or Death). Since we wished to use all exposure data from 2000-2014 and the exposures to each drug had a different exposure profile over time, we needed to correct for this decline in Less Serious Exposures per year.

More Serious Exposures – Linear Model

We calculated the number of More Serious and Less Serious outcomes by year based on our 48 medication subset (single substance human exposures, age 12 and older), N=962,222. Figure 2.1 shows the linear regression for the More Serious cases (solid line) with the 95% CI on the regression fit. Thus the More Serious cases from 2000 through 2014 exhibited a consistent increase.

Figure 2.1 Fit of More Serious Exposures by Year



Linear Fit

More Serious = -1302423 + 654.85357*Year

Summary of Fit

RSquare	0.989368
RSquare Adj	0.98855
Root Mean Square Error	315.0534
Mean of Response	11868.2
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	120073296	120073296	1209.701
Error	13	1290362	99258.646	Prob > F
C. Total	14	121363658		<.0001*

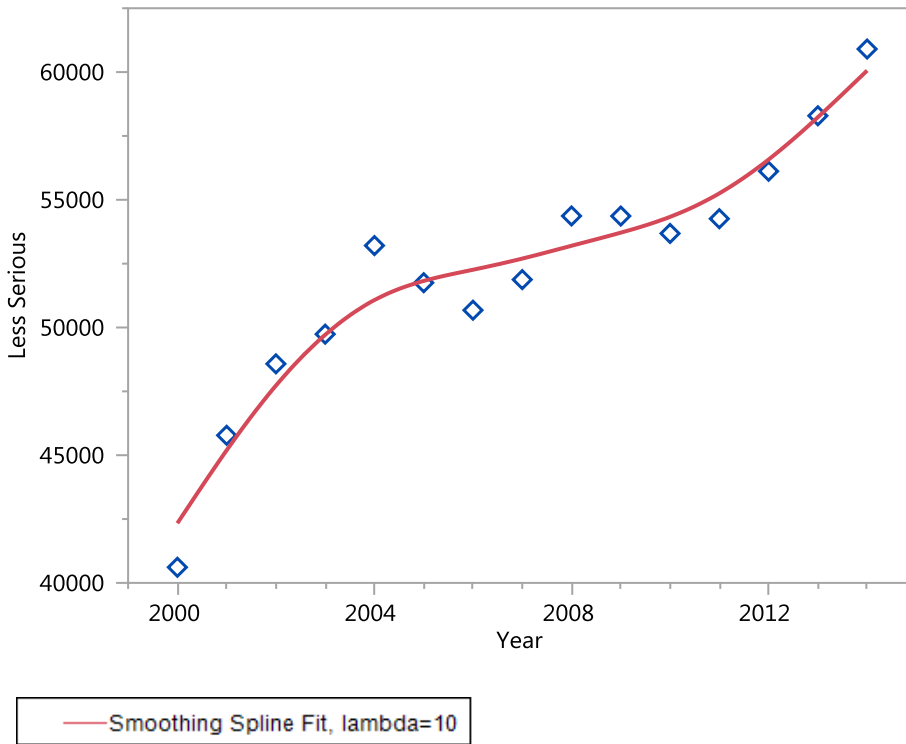
Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob> t	Lower 95%	Upper 95%
Intercept	-1302423	37787.97	-34.47	<.0001*	-1384059	-1220787
Year	654.85357	18.82804	34.78	<.0001*	614.17806	695.52908

Less Serious Exposures – Spline Model

Figure 2.2 shows the Less Serious cases which clearly depart from linearity. The redline shows a spline fit which was chosen to describe the overall change without undue sensitivity to the year to year variability.

Figure 2.2 Spline Fit of Less Serious By Year



Smoothing Spline Fit, lambda=10

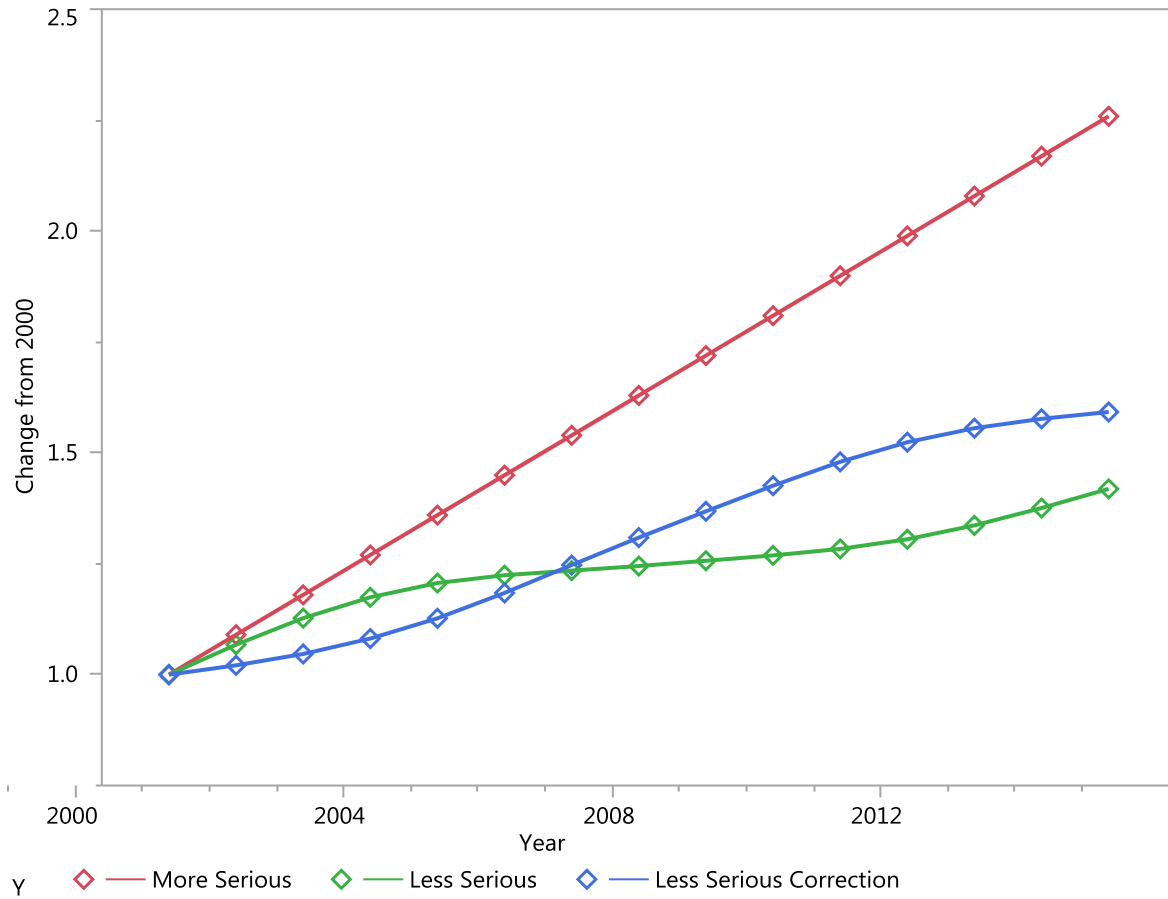
R-Square 0.953551
Sum of Squares Error 15895252

Correction to Less Serious Exposures

We calculated the correction from the change from baseline (Year – 2000) in the More Serious and Less Serious exposures:

$$\text{Less Serious Correction} = \text{More Serious change from 2000} / \text{Less Serious change from 2000}$$

Figure 2.3 Plot of Change from 2000 in More Serious & Less Serious and Correction by Year



Thus our Less Serious Correction applied a factor to each year of the Less Serious exposures to give the same growth profile as the More Serious exposures. The Correction Summary Table below shows the numerical values for each year.

Correction Summary Table

Year	Model Change from 2000			Exposures per year							Model Fit	
	More Severe	Less Severe	Correction	Death	Major	Moderate	More Severe	Less Severe	Total	Total - Corrected	More Severe	Less Severe
2000	1.0000	1.0000	1.0000	44	1140	5942	7126	40612	47738	47738	7284	42335
2001	1.0899	1.0675	1.0210	36	1233	6732	8001	45779	53780	54740	7939	45193
2002	1.1798	1.1273	1.0465	44	1350	7390	8784	48577	57361	59622	8594	47726
2003	1.2697	1.1743	1.0812	34	1374	7890	9298	49739	59037	63077	9249	49715
2004	1.3596	1.2064	1.1270	45	1461	8940	10446	53207	63653	70408	9904	51075
2005	1.4495	1.2241	1.1841	48	1532	8933	10513	51753	62266	71794	10558	51824
2006	1.5394	1.2345	1.2470	43	1634	9482	11159	50677	61836	74354	11213	52262
2007	1.6293	1.2448	1.3089	58	1556	10211	11825	51875	63700	79725	11868	52698
2008	1.7192	1.2566	1.3681	57	1585	10674	12316	54367	66683	86695	12523	53200
2009	1.8091	1.2688	1.4259	47	1665	11096	12808	54363	67171	90323	13178	53714
2010	1.8990	1.2834	1.4797	52	1611	11744	13407	53682	67089	92840	13833	54332
2011	1.9889	1.3051	1.5239	45	1622	12499	14166	54258	68424	96851	14488	55253
2012	2.0788	1.3364	1.5555	51	1838	13169	15058	56118	71176	102351	15142	56577
2013	2.1687	1.3755	1.5766	58	1826	14153	16037	58289	74326	107937	15797	58234
2014	2.2586	1.4187	1.5920	62	1991	15026	17079	60903	77982	114039	16452	60061

Supplemental Material 4 – Clinical Effects by Medication

Supplemental Material 4 provides a complete tabulation of the Clinical Effects by individual medication (drug and combination medications). NPDS includes reports of medical events associated with each exposure from a standard list of 130 clinical events. We examined the rate of medical events (as a percentage of cases) in exposures resulting in serious outcomes. Twenty-one medical events were excluded (we did not include the event category “other,” “puncture wounds” which were unlikely medication related, or medical events for which the highest rate on any single medication was less than 0.15 %). Medical events were grouped by 8 body systems according to the AAPCC classification system.

(see attached .xlsx)