Comparing 102 psychotropic drug regimens for diabetes mellitus risk

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- **TwoFoldChange consulting**
  - Aurélien Mazurie, PhD
- **Iterative Consulting**
  - Daniel Cannon

Data source

- IBM MarketScan® administrative claims database (2003-2015)
  - Commercially insured patients
  - De-identified information on 932,815 US patients with ≥2 BD diagnoses
  - Visits, diagnoses, procedures, medications, lab orders
  - Data transformed to **OMOP Common Data Model**
- Data hosted by UNM HSC CTSC on high-performance server

Manuscripts:

- Published:
  - A Nestsiarovich, B Kerner, A J Mazurie, D C Cannon, N G Hurwitz, Y Zhu, S J Nelson, T I Oprea, M L Unruh, AS Crisanti, M Tohen, DJ Perkins, CG Lambert. **Comparison of 71 bipolar disorder pharmacotherapies for kidney disorder risk: The potential hazards of polypharmacy. Journal of Affective disorders.** 2019 Jan; 252:201-2011.
  - Nestsiarovich A, Mazurie AJ, Hurwitz NG, Kerner B, Nelson SJ, Crisanti AS, Tohen M, Krall RL, Perkins DJ, Lambert CG. **Comprehensive comparison of monotherapies for psychiatric hospitalization risk in bipolar disorders.** Bipolar Disord. 2018 Dec;20(8):761-771.

- Accepted for publication:
  - Praveen Kumar, Anastasiya Nestsiarovich, Stuart J. Nelson, Berit Kerner, Douglas J. Perkins, Christophe G. Lambert. **Imputation and characterization of uncoded self-harm in major mental illness using machine learning**. JAMIA journal (accepted 05 Sept. 2019).

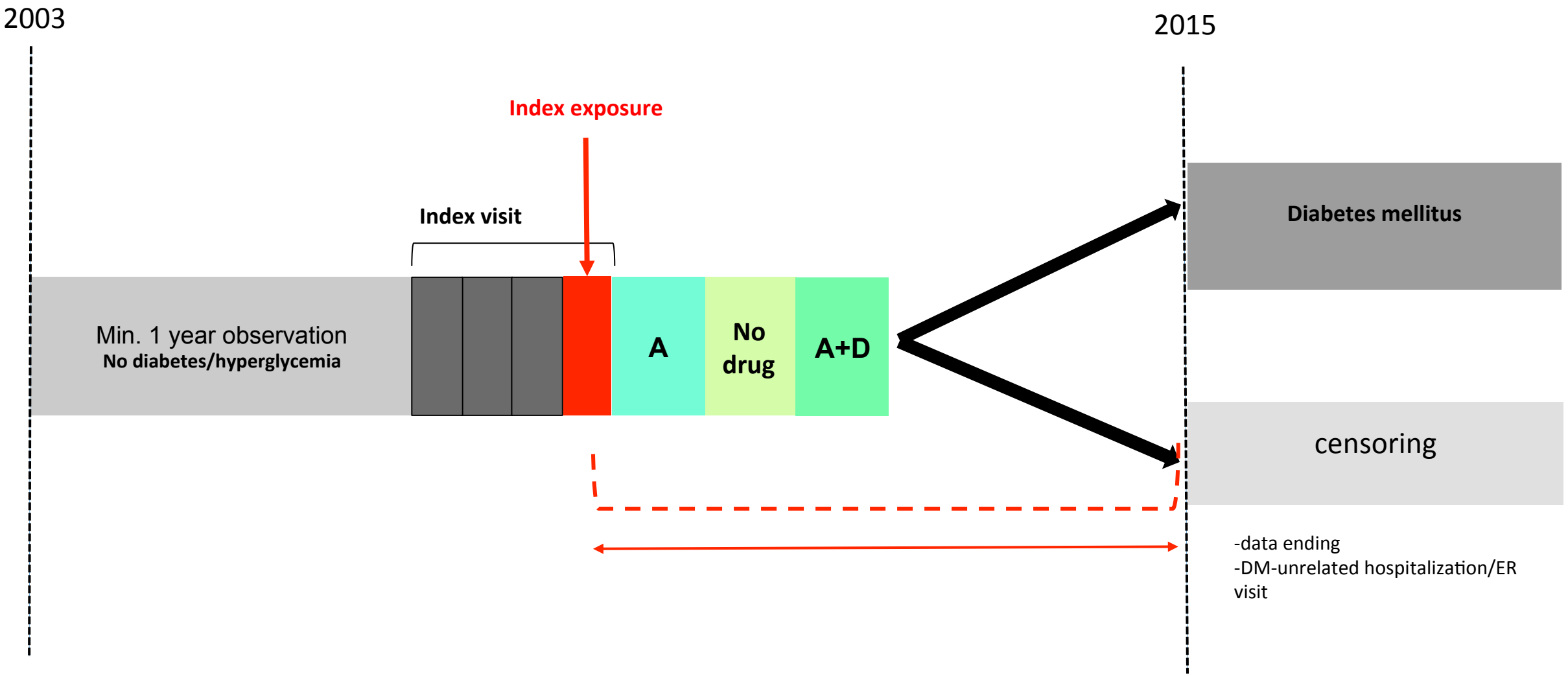
- **Under review:**
  - Anastasiya Nestsiarovich, Berit Kerner, Aurélien J. Mazurie, Daniel C. Cannon, Nathaniel G. Hurwitz, Yiliang Zhu, Stuart J. Nelson, Tudor I. Oprea, Annette S. Crisanti, Mauricio Tohen, Douglas J. Perkins, Christophe G. Lambert, Ph.D. **Diabetes mellitus risk for 102 drugs and drug combinations used in patients with bipolar disorder.** Psychoneuropharmacology (submitted 27 Aug 2019).

Design and analysis:

- **Inclusion criteria:**
  - Age **18-64** years
  - **≥2 ICD codes for BD** (296.[0-1]*, 296.[4-8]*, F30*, F31*) during 2003-2015.
  - **Received BD medication(s)** at least once following the index visit

- **Exclusion criteria:**
  - **Diagnosis** of schizophrenia, schizoaffective disorder, chronic delusional disorders, intellectual disabilities, autism spectrum disorders, mental illness of organic origin, or Parkinson's disease at any time during the observation period
  - Received **anti-dementia drugs** at any time point
  - Received **insulin or were diagnosed with any glucose metabolism-related disorder**, including DM and pancreatic disorders, prior to index exposure

Design:


2003
2015
Index exposure
Index visit
Min. 1 year observation
No diabetes/hyperglycemia
A
No drug
A+D
Diabetes mellitus
censoring
-data ending
-DM-unrelated hospitalization/ER visit

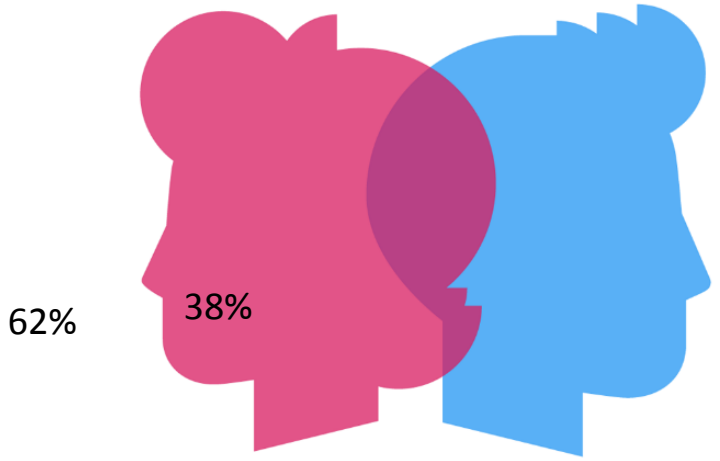
Design and analysis:

- Drug regimen: ≥ 1000 treatment intervals, ≥5 DM outcomes.
  - 659 regimens →19 monotherapies + 83 combinations
  - **Individual** therapies: lithium, MSAs, SGAs, TGA
  - **Classes**: FGAs, antidepressants
  - **Multi-class** polypharmacies: 2, 3, and 4+ classes

- Cox regression model with time-varying covariates
  - 102 regimens **with "no drug" as a reference**
  - 85 pre-treatment covariates

Diabetes mellitus (DM) study: results

- Total: 565,253 adults fit criteria
- 4.1% had a new DM (N=22,951).
- Annual incidence of new-onset DM 3.09% (general US population 0.32-0.88%)
  - mean of **342.7 days** (median 136) after the index visit
  - **741,573 years** of observation under the drug regimens studied



Diabetes mellitus regression analysis

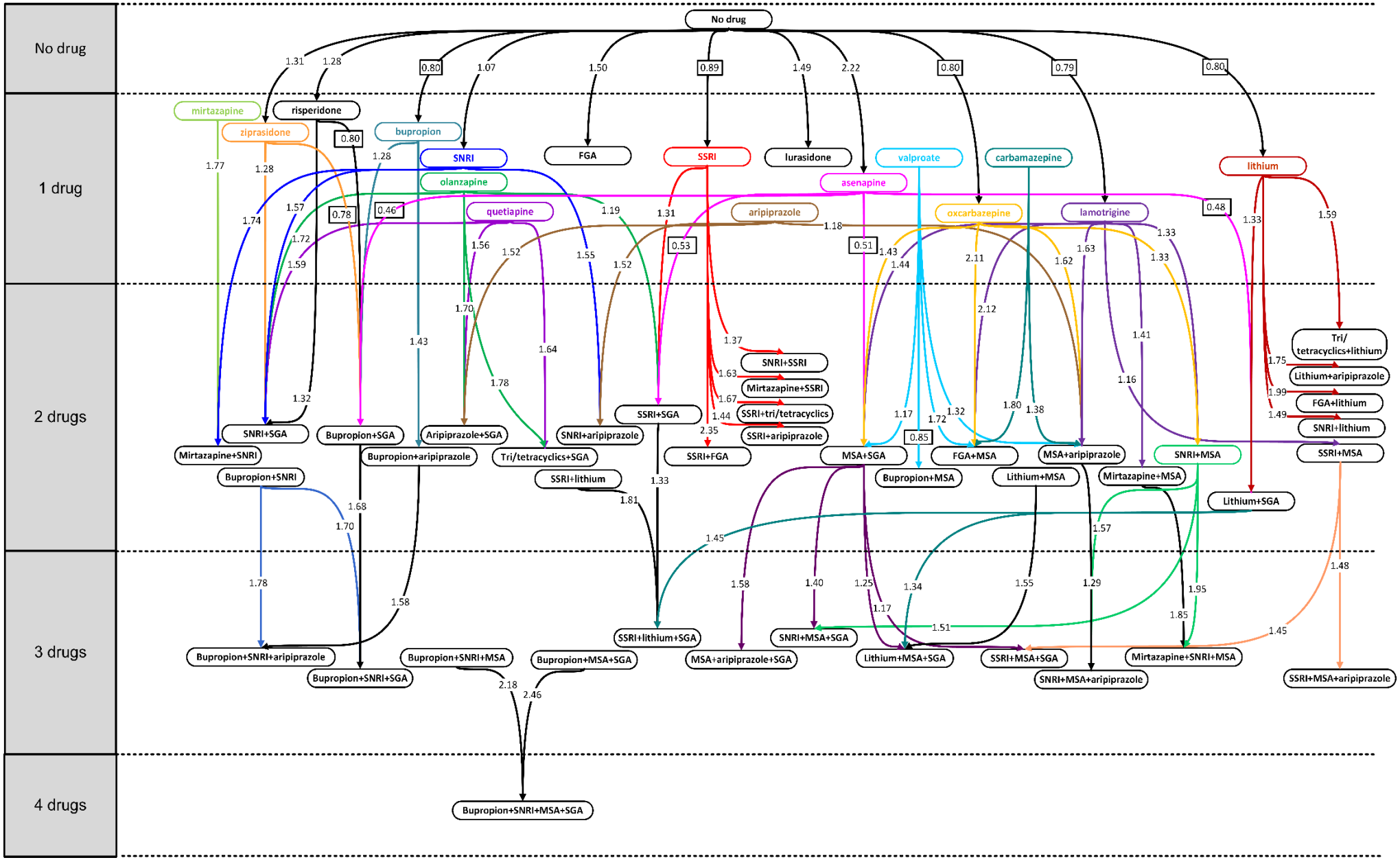
39 regimens had HR>1 with p<0.05

Covariate	HR	p-value	Lower limit 95%CI	Upper limit 95%CI	N-patients	N-intervals
Drug regimens						
NDRI+SNRI+MSA+SGA	2.37	5.38×10^{-6}	1.62	3.46	941	1,533
Uncommon monotherapy	2.32	2.47×10^{-3}	1.33	4.04	521	876
asenapine monotherapy	2.22	2.70×10^{-4}	1.43	3.43	1,579	2,385
SSRI+MSA+TGA+SGA	2.18	3.64×10^{-3}	1.27	3.72	809	1,151
SSRI+FGA	2.09	3.42×10^{-5}	1.46	2.97	1,073	1,601
SNRI+SSRI+TGA	2.08	6.16×10^{-3}	1.22	3.56	736	1,012
NASSA+SNRI+MSA	2.07	3.74×10^{-3}	1.25	3.41	716	1,032
NASSA+SNRI	1.86	3.05×10^{-3}	1.22	2.82	1,396	1,972
MSA+TGA+SGA	1.81	4.04×10^{-4}	1.29	2.52	2,339	3,693
NDRI+SNRI+TGA	1.79	1.46×10^{-3}	1.24	2.58	1,187	2,007
multiSGA	1.77	2.04×10^{-4}	1.30	2.40	3,368	4,733
SNRI+SSRI+MSA+SGA	1.74	4.65×10^{-2}	1.00	3.03	889	1,293
Tri/tetracyclics+SGA	1.73	1.66×10^{-2}	1.09	2.75	1,113	1,655
NDRI+SNRI+SGA	1.71	1.15×10^{-3}	1.23	2.38	1,722	2,812
FGA+MSA	1.68	2.44×10^{-4}	1.27	2.24	1,869	3,056
SNRI+SGA	1.68	6.12×10^{-24}	1.52	1.86	18,655	31,326
SNRI+lithium+TGA	1.68	8.55×10^{-2}	0.92	3.07	715	1,095
SNRI+MSA+TGA	1.66	6.85×10^{-7}	1.35	2.03	4,374	7,432
SNRI+TGA	1.66	3.51×10^{-12}	1.43	1.91	10,089	16,880
TGA+SGA	1.66	1.48×10^{-3}	1.21	2.27	3,535	5,148
Polypharmacy2	1.60	6.67×10^{-5}	1.27	2.03	3,832	6,516
SNRI+MSA+SGA	1.59	2.33×10^{-11}	1.39	1.83	9,670	16,562
FGA+lithium	1.59	1.96×10^{-3}	1.18	2.15	1,015	1,865
SSRI+lithium+SGA	1.55	6.08×10^{-5}	1.25	1.93	4,729	7,989
FGA mono-class therapy	1.50	4.20×10^{-4}	1.19	1.89	3,817	6,337

Diabetes mellitus regression analysis (cont.)

Covariate	HR	p-value	Lower limit 95%CI	Upper limit 95%CI	N-patients
SSRI+MSA	**0.92**	**1.67 x10^{-2}**	**0.85**	**0.99**	**68,565**
NASSA+TGA	0.90	8.13 x10^{-1}	0.37	2.20	750
SSRI mono-class therapy	**0.89**	**2.12 x10^{-5}**	**0.84**	**0.94**	**144,353**
NDRI+lithium+MSA	0.88	5.83 x10^{-1}	0.56	1.38	1,929
NDRI+SSRI+MSA	0.88	2.08 x10^{-1}	0.72	1.08	8,300
NDRI+lithium	0.86	2.14 x10^{-1}	0.68	1.09	5,769
SSRI+lithium	**0.86**	**3.31 x10^{-2}**	**0.74**	**0.99**	**15,068**
NDRI+lithium+SGA	0.84	4.59 x10^{-1}	0.52	1.35	1,714
NDRI+MSA	**0.83**	**1.36 x10^{-3}**	**0.75**	**0.93**	**27,347**
NDRI+SSRI	**0.83**	**2.05 x10^{-2}**	**0.70**	**0.97**	**15,861**
lithium monotherapy	**0.80**	**2.39 x10^{-9}**	**0.74**	**0.86**	**54,944**
NDRI (bupropion only) monotherapy	**0.80**	**4.29 x10^{-6}**	**0.72**	**0.88**	**50,277**
oxcarbazepine monotherapy	**0.80**	**6.89 x10^{-3}**	**0.67**	**0.94**	**18,009**
lamotrigine monotherapy	**0.79**	**1.16 x10^{-3}**	**0.75**	**0.85**	**121,730**
NDRI+SSRI+lithium	0.77	3.05 x10^{-1}	0.46	1.29	1,533
NASSA+NDRI	0.73	4.77 x10^{-1}	0.30	1.78	759
NDRI+lithium+MSA+SGA	0.66	3.05 x10^{-1}	0.29	1.49	706
NASSA+MSA+SGA	0.57	1.63 x10^{-1}	0.25	1.28	1,021

Multi-drug analysis



Conclusions:

1. DM risk varied **3-fold** among different regimens.
2. **Lower DM risk** for lithium, lamotrigine, oxcarbazepine, and bupropion monotherapies, SSRI mono-class therapy, and bupropion- and SSRI-containing drug combinations.
3. **Psychotropic polypharmacy** was often associated with higher risk of DM compared to monotherapies.
4. The majority of **antipsychotic-**containing regimens were associated with a significantly higher risk of DM versus “No drug”.

Limitations of the study:

- Non-randomized assignment of patients to treatment groups,
- No data were available prior to insurance enrollment data or 2003 (baseline risk for DM could differ)
- Unmeasured indication or other biases could remain that distort drug risk estimates for DM (family history, ethnicity, lifestyle).
- No correction was made for the number of drugs of interest used prior, current drug dosage, route of administration, or release mechanism.
- "No drug" chosen as a comparator - indication bias can exist