Supplementary Online Content

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eMethods. Detailed Methodology

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

eMethods. Detailed Methodology

The equation listed below summarizes our ITSA model specifications:

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \varepsilon_t$$

where Y_t is the monthly aggregated number of incident prescriptions dispensed measured in month t, Tt is the time since the start of study period (in months) by the time of month t, X_t is a dummy (indicator) variable representing if the month is in the COVID-19 pandemic period (April 2020 onwards) or not, and $X_t T_t$ is an interaction term. β_0 represents the intercept or starting level of the outcome variable. β_1 is the trajectory(slope) of the outcome variable until the start of COVID-pandemic. The model allows to test for both a one-time immediate level change at the start of the COVID-pandemic (intercept; β2) and the difference in the pre- and post-pandemic trends in the outcomes (slope; β3).

eTable 1. Total (Prevalent) Prescriptions Dispensed by Selected USC Drug Classes and Drugs, April 2018 – March 2022[a]

USC Drug Class and Drug	Prescriptions	%	USC Drug Class and Drug	Prescriptions	%
64300 Antidepressants	1,154,655,246	100%	64500 Analeptics	276,029,760	100%
64340 SSRI	576,743,650	50%	Amphetamine/Dextroamphetamine	149,321,137	54%
Sertraline	180,369,088	31%	Methylphenidate	58,588,537	21%
Escitalopram	150,410,750	26%	Lisdexamfetamine	46,134,257	17%
Fluoxetine	114,863,177	20%	Dexmethylphenidate	17,295,687	6%
Citalopram	85,671,171	15%	Dextroamphetamine	3,008,406	1%
Paroxetine	41,100,267	7%	Amphetamine	1,634,660	1%
Fluvoxamine	4,329,195	1%	Methamphetamine	32,556	<1%
64330 Newer Generation Antidepressants	262,642,007	23%	Dexmethylphenidate/Serdexmethylphenidate	14,519	<1%
Bupropion	138,635,544	53%	64610 Benzodiazepines	249,097,466	100%
Trazodone	123,727,523	47%	Alprazolam	138,212,370	55%
Nefazodone	278,939	<1%	Lorazepam	72,019,106	29%
64350 SNRI	190,171,185	16%	Diazepam	35,320,004	14%
Duloxetine	97,401,830	51%	Chlordiazepoxide	1,706,774	1%
Venlafaxine	78,165,486	41%	Clorazepate	1,324,673	1%
Desvenlafaxine	13,917,219	7%	Oxazepam	472,915	<1%
Levomilnacipran	686,651	<1%	Midazolam	41,623	<1%
64310 Tricyclics & Tetracyclics	110,826,157	10%	64700 Newer Generation Psychotherapy Agents[b]	26,844,341	100%
Amitriptyline	46,368,017	42%	Guanfacine ER	14,610,920	54%
Mirtazapine	36,076,677	33%	Atomoxetine	10,728,838	40%
Nortriptyline	14,131,352	13%	Clonidine ER	1,408,606	5%
Doxepin	9,708,387	9%	Viloxazine ER	95,977	<1%
Imipramine	2,471,382	2%	78340 Drug Dependence (MOUD)	62,718,516	100%
Clomipramine	1,244,369	1%	Buprenorphine/Naloxone	52,914,497	84%
Desipramine	676,666	1%	Buprenorphine	9,804,019	16%
Protriptyline	109,430	<1%			
Amoxapine	18,327	<1%			
Maprotiline	12,049	<1%			
Trimipramine	9,500	<1%			
64360 SSRI/5-HT Partial Agonists	13,842,816	1%			
Vortioxetine	8,503,920	61%			
Vilazodone	5,338,896	39%			
64320 MAO Inhibitors	242,224	<1%			
Phenelzine	122,233	50%			
Tranylcypromine	117,872	49%			

Isocarboxazid	2,119	1%
64380 Antidepressant In Combination	187,207	<1%
Amitriptyline/Chlordiazepoxide	99,278	53%
Amitriptyline/Perphenazine	87,928	47%

Abbreviation: USC, Uniform System of Classification, developed by IQVIA™; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin–norepinephrine reuptake inhibitor; MOUD, medications for opioid use disorder; 5-HT, 5-hydroxytryptamine (serotonin); MAO, monoamine oxidase

[a] Source: IQVIA National Prescription Audit™. April 2018 – March 2022. Extracted April 2023. Limited to oral formulations; other formulations (e.g., injection, implants) were not included. Data are provided for nationally estimated drug products labeled for mental health conditions, (e.g., guanfacine ER products labeled for ADHD, buprenorphine products labeled for MOUD treatment). Excludes prescriptions written by Veterinary Medicine. Only selected drugs from these USC Drug Class were included: only C-II stimulants were included from USC 64500; only buprenorphine-naloxone and buprenorphine MOUD products were included from USC 78340. Buprenorphine-containing products and methadone are approved for MOUD; however, methadone was not included as methadone for OUD is only available from opioid treatment programs. Methadone and buprenorphine products labeled for analgesia were excluded from our study. Only benzodiazepines from USC drug class 64610 were included because they are commonly used for anxiety in the outpatient setting unlike benzodiazepines in other USC drug classes.

[b] Newer Generation Psychotherapeutic Agents are referred to as "non-stimulant ADHD drugs" in our study.

eTable 2. Interrupted Time-Series Regression Sensitivity Analyses of Monthly Incident[a] Prescriptions Dispensed (in Thousands) for Selected Drug Classes and Drugs, before and during the COVID-19 Pandemic[b]

Drug Class / Drug	Intercept (04/2018)	Pre-COVID-19 Pandemic (04/2018 – 02/2020)		Level Change Associated With COVID-19 Pandemic (05/2020)		During COVID-19 Pandemic (05/2020 – 03/2022)		Slope Change Associated With COVID-19 Pandemic	
	Intercept (95% CI)	Slope[d] (95% CI)	P Value	Level Change (95% CI)	P Value	Slope[d] (95% CI)	P Value	Slope Change (95% CI)	P Value
Antidepressants	1144.030 (1083.799 – 1204.261)	6.589 (1.107 – 12.070)	0.020*	-49.055 (-173.451 – 75.340)	0.431	7.874 (2.121 – 13.627)	0.008*	1.285 (-6.661 – 9.231)	0.746
Sertraline	202.353 (191.697 – 213.008)	1.667 (0.717 – 2.618)	0.001*	-8.868 (-31.779 – 14.043)	0.439	1.519 (0.345 – 2.693)	0.012*	-0.149 (-1.659 – 1.362)	0.843
Escitalopram	172.778 (163.835 – 181.720)	1.728 (0.906 – 2.552)	<0.001*	-1.284 (-22.296 – 19.729)	0.902	1.706 (0.541 – 2.871)	0.005*	-0.022 (-1.449 – 1.404)	0.975
Benzodiazepines	59.458 (639.649 – 679.266)	-2.783 (-4.306 – -1.261)	0.001*	-7.906 (-44.341 – 28.530)	0.664	-0.542 (-2.632 – 1.549)	0.604	2.242 (-0.344 – 4.828)	0.088
Alprazolam	250.241 (242.120 – 258.361)	-1.174 (-1.832 – -0.517)	0.001*	-4.713 (-18.221 – 8.796)	0.485	-0.235 (-0.882 – 0.413)	0.468	0.939 (0.017 – 1.862)	0.046*
Lorazepam	201.630 (195.862 – 207.399)	-0.560 (-1.023 – -0.098)	0.019*	0.355 (-9.865 – 10.576)	0.944	-0.029 (-0.584 – 0.527)	0.917	-0.531 (-0.192 – 1.254)	0.917
C-II Stimulant	198.675 (171.887 – 225.464)	1.739 (-0.358 – 3.835)	0.102	-54.402 (-94.729 – -14.074)	0.009*	5.623 (4.067 – 7.179)	<0.001*	3.884 (1.273 – 6.495)	0.005*
Amphetamine-Dextroamphetamine	99.489 (90.013 – 108.965)	0.683 (0.087 – 1.453)	0.081	-17.852 (-32.968 – -2.735)	0.022*	2.925 (2.348 – 3.502)	<0.001*	2.242 (1.280 – 3.205)	<0.001*
Methylphenidate	49.893 (39.787 – 59.999)	0.620 (-0.142 – 1.383)	0.108	-19.408 (-33.792 – -5.024)	0.009*	1.534 (0.952 – 2.116)	<0.001*	0.914 (-0.045 – 1.874)	0.061
Non-stimulant ADHD Drugs	35.735 (32.269 – 39.202)	0.634 (0.358 – 0.910)	<0.001*	-13.211 (-19.030 – -7.393)	<0.001*	1.725 (1.379 – 2.071)	<0.001*	1.090 (0.648 – 1.533)	<0.001*
Atomoxetine	20.381 (18.841 – 21.920)	0.344 (0.217 – 0.472)	<0.001*	-5.527 (-8.519 – -2.536)	0.001*	1.105 (0.915 – 1.296)	<0.001*	0.761 (0.532 – 0.990)	<0.001*

Guanfacine ER	14.383 (12.158 – 16.607)	0.274 (0.102 – 0.446)	0.002*	-6.794 (-10.113 – -3.474)	<0.001*	0.437 (0.277 – 0.596)	<0.001*	0.162 (-0.072 – 0.396)	0.170
Buprenorphine MOUD[c]	36.986 (35.421 – 38.551)	0.143 (0.002 – 0.284)	0.047*	-2.791 (-5.735 – 0.154)	0.063	0.015 (-0.116 – 0.145)	0.823	-0.129 (-0.321 – 0.064)	0.184

Abbreviation: 95% CI, 95% Confidence interval; ADHD, attention deficit hyperactivity disorder; ER, extended-release; MOUD, medications for opioid use disorder

[a] Incident prescription is measured by new therapy start prescriptions, defined as prescriptions for a drug dispensed to patients with no prior prescription dispensed for a drug within the same drug class (e.g., USC 64300 Antidepressants) in the previous 12 months.

[b] Data Source: IQVIA National Prescription Audit™. April 2018 – March 2022 (Data from March 2020 and April 2020 were excluded for sensitivity analyses). Extracted March 2023. Limited to oral formulations; other formulations (e.g., injection, implants) were not included. Nationally estimated data are provided for drug products labeled for mental health conditions, (e.g., guanfacine ER products labeled for ADHD, buprenorphine-containing products labeled for opioid use disorder treatment). Prescriptions written by veterinary medicine, and prescriptions dispensed for unspecified patient age or gender were excluded. Except where specified, drugs include long-acting and short-acting formulations.

[c] Buprenorphine-containing products and methadone are approved for MOUD, methadone was not included as methadone for opioid use disorder is only available from OTP opioid treatment programs, only methadone for analgesia is through pharmacies. Only buprenorphine MOUD products (buprenorphine and buprenorphine/naloxone) labeled for the treatment of opioid use disorder were included in this drug class for our analyses.

[d] Slope coefficient is the estimated number of increases in NTS prescription in thousands per month; We used Prais–Winsten regression with the Cochrane–Orcutt transformation and robust SEs to adjust for first-order serial autocorrelation.

The COVID-19 outbreak in the United States constitutes a national emergency, beginning March 1, 2020.

*Indicates the results are significant at 95% level.