

Supplementary Table 1. Weighted demographic characteristics of U.S. adults

Characteristic	Category	n	Weighted % (95% CI)
Age group	18-49	4706	53.85 (51.36-56.34)
	50-64	2576	25.73 (24.24-27.22)
	65+	2411	20.42 (18.20-22.64)
Sex	Male	4718	48.23 (46.70-49.77)
	Female	4975	51.77 (50.23-53.30)
Race/Ethnicity (RIDRETH1)	Mexican American	1131	8.60 (6.36-10.84)
	Other Hispanic	991	7.73 (6.29-9.16)
	Non-Hispanic White	3370	62.18 (57.43-66.92)
	Non-Hispanic Black	2555	11.46 (8.67-14.26)
	Other race (including multi-racial)	1646	10.03 (8.05-12.02)

Percentages are weighted using NHANES interview weights (WTINTPRP). 95% CIs were calculated using Taylor-series linearization with strata (SDMVSTRA) and PSUs (SDMVPSU). Abbreviations: CI = Confidence Interval; n = Number of Cases; NHANES = National Health and Nutrition Examination Survey; PSU = Primary Sampling Unit; SDMVPSU = Survey Design Variable Primary Sampling Unit; SDMVSTRA = Survey Design Variable Stratum; WTINTPRP = Interview Sample Weight.

Supplementary Table 2. Prevalence of potential clinically significant DDIs by polypharmacy status

Group / Outcome	Unweighted n	Weighted %	95% CI
Polypharmacy (≥5 valid meds)			
Any Tier 1 contraindicated medication	446	22.362	18.961-25.764
Any Tier 2 medication requiring avoidance/hold/dose adjustment/monitoring	1522	79.544	76.829-82.260
Any Tier 1 or Tier 2 medication	1655	86.502	83.620-89.384
Non-Polypharmacy (<5 valid meds)			
Any Tier 1 contraindicated medication	302	3.680	2.750-4.610
Any Tier 2 medication requiring avoidance/hold/dose adjustment/monitoring	1435	17.037	15.676-18.398
Any Tier 1 or Tier 2 medication	1649	19.751	18.107-21.394

Unweighted n indicates the number of participants in the analytic sample meeting the criterion. Weighted percentages and 95% confidence intervals (CIs) reflect the non-institutionalized U.S. adult population using NHANES complex survey design. Tier definitions follow the study's FDA Table-based DDI dictionary (Tier 1: contraindicated; Tier 2: avoid/hold/dose adjust/monitor). Polypharmacy was defined as ≥5 concurrent valid prescription medications in the NHANES prescription inventory.

Abbreviations: CI = Confidence Interval; DDI = Drug-Drug Interaction; FDA = Food and Drug Administration; NHANES = National Health and Nutrition Examination Survey.

Supplementary Table 3. Top 10 Most Prevalent Tier 1 Contraindicated Medication Ingredients Among U.S. Adults, NHANES 2017-March 2020 (Pre-Pandemic)

Medication (Generic Name)	Unweighted n	Weighted Prevalence (%)	95% Confidence Interval
Simvastatin	485	4.27	3.35-5.19
Lovastatin	79	0.84	0.49-1.19
Colchicine	26	0.27	0.09-0.45
Carbamazepine	14	0.21	0.02-0.41
Lurasidone	12	0.21	0.05-0.37
Amiodarone	30	0.17	0.08-0.27
Sildenafil	22	0.15	0.04-0.27
Alfuzosin	11	0.14	0.05-0.24
Dronedarone	5	0.12	-0.02-0.27
Flecainide	12	0.12	0.03-0.21

Tier 1 agents are medications contraindicated with nirmatrelvir/ritonavir (Paxlovid) per the FDA Paxlovid Fact Sheet for Healthcare Providers, defined as those for which co-administration is expected to produce serious or life-threatening toxicity or significant loss of virologic response. Prevalence estimates and 95% CIs were derived using NHANES complex survey procedures (Taylor Series linearization), applying the MEC examination survey weights for NHANES 2017-March 2020 pre-pandemic data. Unweighted n reflects the number of survey participants reporting use of the specified ingredient. The negative lower CI bound for dronedarone reflects statistical uncertainty around a small cell estimate (unweighted n = 5) and should be interpreted with caution. Ingredients were identified via exact match to the FDA interaction table using a structured DDI dictionary.

Abbreviations: CI = Confidence Interval; DDI = Drug-Drug Interaction; FDA = Food and Drug Administration; MEC = Mobile Examination Center; NHANES = National Health and Nutrition Examination Survey.

Supplementary Table 4. Sensitivity analysis restricted to interviewer-observed prescriptions (RXQSEEN = 1)

Outcome	Unweighted n	Weighted %	95% CI
Any Tier 1 contraindicated medication	663	6.075	4.825-7.325
Any Tier 2 medication requiring avoidance/hold/dose adjustment/monitoring	2659	24.857	23.280-26.434
Any Tier 1 or Tier 2 medication	2978	28.045	26.076-30.014

Unweighted n indicates the number of participants in the analytic sample meeting the criterion. Weighted percentages and 95% confidence intervals (CIs) reflect the non-institutionalized U.S. adult population using NHANES complex survey design. Tier definitions follow the study's FDA Table-based DDI dictionary (Tier 1: contraindicated; Tier 2: avoid/hold/dose adjust/monitor). The sensitivity analysis restricts medication ascertainment to prescriptions verified as seen by the interviewer.

Abbreviations: CI = Confidence Interval; DDI = Drug-Drug Interaction; FDA = Food and Drug Administration; NHANES = National Health and Nutrition Examination Survey; RXQSEEN = Prescription Seen by Interviewer.