

CARDIAC SAFETY

Oral Contraceptive Use and the ECG: Evidence of an Adverse QT Effect on Corrected QT Interval

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Background: A prolonged corrected QT (QTc) interval is a marker for an increased risk of sudden cardiac death. We evaluated the relationship between oral contraceptive (OC) use, type of OC, and QTc interval.

Methods: We identified 410,782 ECGs performed at Northern California Kaiser Permanente on female patients between 15 and 53 years from January, 1995 to June, 2008. QT was corrected for heart rate using log-linear regression. OC generation (first, second and third) was classified by increasing progestin androgenic potency, while the fourth generation was classified as antiandrogenic.

Results: Among 410,782 women, 8.4% were on OC. In multivariate analysis after correction for comorbidities, there was an independent shortening effect of OCs overall (slope = -0.5 ms; SE = 0.12, $P < 0.0002$). Users of first and second generation progestins had a significantly shorter QTc than nonusers ($P < 0.0001$), while users of fourth generation had a significantly longer QTc than nonusers (slope = 3.6 ms, SE = 0.35, $P < 0.0001$).

Conclusion: Overall, OC use has a shortening effect on the QTc. Shorter QTc is seen with first and second generation OC while fourth generation OC use has a lengthening effect on the QTc. Careful examination of adverse event rates in fourth generation OC users is needed.

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QT; hormones

INTRODUCTION

A prolonged heart-rate corrected QT (QTc) interval is a marker for an increased risk of ventricular tachyarrhythmias, specifically torsades de pointes (TdP) and sudden cardiac death (SCD).¹ Both endogenous and exogenous sex hormones have been shown to affect the QTc interval.^{2–7} Endogenous testosterone and progesterone shorten the action potential^{4,5,7} while estrogen lengthens the QTc interval.⁶ Studies of menopause replacement therapy (MHT) in the form of estrogen-alone therapy (ET) and estrogen plus progesterone therapy (EPT) have suggested a counterbalancing effect of exogenous estrogen and progesterone on the QTc.

Specifically, ET lengthens the QTc while EPT has no effect.^{2,3}

To date, no study has been performed on the overall effect of oral contraception (OC) on the QTc interval and of the effect of different generations of OC on the QTc. Four generations of OC by progestin type have been developed: first and second generation OCs have progestins that are androgenic with relatively high levels of estrogen. Third generation OCs have progestins that are less androgenic while fourth generation are non-testosterone derived and antiandrogenic. Because estrogen lengthens the QTc, while testosterone and progesterone shorten ventricular repolarization, we hypothesized that

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fourth generation OCs would be associated with a longer QTc.

The primary aim of this study was to evaluate the relationship between oral contraceptive (OC) use, generation of OC, and QTc interval in a cohort of healthy premenopausal women. As a secondary aim, we chose to evaluate the relationship between QTc and mode of contraceptive delivery (oral, transvaginal, or transdermal) and between QTc and estrogen dose.

METHODS

Kaiser Permanente of Northern California (KPNC) is an integrated health care delivery system serving 3.3 million members and offers comprehensive inpatient and outpatient care to its members. It captures many aspects of clinical care through multiple comprehensive clinical and administrative databases and is broadly representative of the Northern California population.⁸

Historically, all of the waveforms and associated ECG output including automatic QT and RR measurements were archived locally at each KPNC medical center. To enable this study, all of these ECG electronic records (including multiple ECGs per person sorted by date and time) were consolidated into a central database at the KP Division of Research. Five point seven million 12-lead ECG tracings from 1.8 million Northern California Kaiser Permanente members were obtained between 1995 and 2008. ECG tracings with evidence of pacemakers ($n = 104,478$), or with QTc ($n = 1015$) or heart rate ($n = 18,330$) out of physiological range (i.e., QTc < 200 ms or > 800 ms and heart rate < 40 bpm or > 180 bpm) were sequentially excluded, resulting in 5,709,441 ECG tracings in 1,783,776 persons. In addition, a subset database with person as the level of analyses (the index ECG) was created by selecting all ECGs among persons with only one ECG and one ECG at random among persons with more than one ECG. Specifically, for patients with more than one ECG, one ECG was selected at random and we denoted this ECG as the index "ECG." We further narrowed our field of interest to the index ECG in women between the ages of 15–53 years and obtained 410,782 ECGs. Next, we separated these index ECGs into those in women on OC and those in women off OC at the time of the index ECG. The study was approved by the Kaiser

Foundation Research Institute Institutional Review Board.

QT Measurement and Adjustment for Heart Rate

All ECGs at KPNC were obtained using cardiographs manufactured by Philips Medical Systems (Andover, MA, USA). For this study, we extracted the raw QT and RR measurements that were generated from each 12-lead waveform by the proprietary Philips algorithms (software version PH07 through 2005 and PH08 in 2006–08), which are described elsewhere.⁹ Because of their limitations (particularly in the case of bradycardia),¹⁰ we did not use the Bazett's or Fridericia formulas for heart rate correction. Instead we performed, using the index ECG, log-linear regression of raw QT on RR as described by Malik et al. and then fitted a correction equation within 28 strata of gender (2 groups), age (7 groups) and race/ethnicity (7 groups) to produce gender-age-race/ethnicity heart rate-corrected by regression QT values (denoted by QTc throughout the article).¹¹

DEFINITIONS OF ORAL CONTRACEPTIVES

OC generations were defined according to Table 1. Estrogen dose was defined as very low dose (20–25 mcg delivered per day), low dose (30–35 mcg delivered per day), and moderate dose (50 mcg delivered per day). Mode of contraceptive delivery was categorized into oral, transvaginal, or transdermal preparations.

Statistical Analysis

Baseline characteristics stratified by OC use were compared using *t*-tests for continuous variables and the chi-square and Fisher's exact tests for categorical variables. We obtained univariate statistics for QTc in OC users and OC nonusers using ANOVA. In addition, we obtained univariate statistics for QTc by OC generation in OC users and OC nonusers using ANOVA. Multivariate analysis was obtained using multivariable linear regression adjusting for age, race, smoking and the following comorbidities: hypertension, diabetes, hyperlipidemia, prior cardiac arrest, end stage renal failure, heart failure, prior acute coronary

Table 1. Classification of Oral Contraceptive Generations by Progestin Androgenicity

	Progestin	Androgenicity
First generation	Norethindrone or ethynodiol	Androgenic
Second generation	Levonorgestrel or norgestrel	Androgenic
Third generation	Norgestimate, norelgestromin, desogestrel, or etonogestrel	Less androgenic
Fourth generation	Drospirenone	Antiandrogenic

syndrome, prior ventricular dysrhythmia, obesity, prior transient ischemia attack, prior hemorrhagic stroke, and prior ischemic stroke. The results were then stratified by comorbidity (defined as the presence of one or more of the comorbidities listed above) and exposure to QTc-altering medications (see Appendix A for list of QTc prolonging medications). All statistical analyses were performed using SAS release 9.13 (SAS Institute, Cary, NC, USA).

RESULTS

Among 410,782 women, 8.4% (34, 676) were on OC. Women taking OC were younger (33.2 vs. 40.7 years), more likely to be Caucasian, less likely to smoke, and had less comorbidity than unexposed women ($P < 0.0001$) (Table 2).

In univariate analysis by ANOVA, women taking OC had an almost 4 ms shorter QTc ($400.8 \text{ ms} \pm 21.3$) than women not taking OC ($403.5 \text{ ms} \pm 22.6$) ($P < 0.0001$). There was also a statistically significant difference in QTc when examined by OC generation, dose, and route of delivery among OC users compared to OC nonusers (all P -values < 0.0001). However, when nonusers were removed, only OC generation remained statistically significant with an almost 4 ms longer QTc amongst fourth generation OC users (403.5 ms) as compared to first, second and third generation OC users (400.8 ms , 399.2 ms , and 400.8 ms , respectively) ($P < 0.0001$) (Table 3). In contrast, both dose and route of delivery became nonsignificant after OC nonusers were removed ($P = 0.19$ and $P = 0.49$, respectively) (Table 3).

In multivariate analysis using linear regression, after correction for age, race, smoking and comorbidity, OC users continued to have a shorter QTc than nonusers (slope = -0.5 ms ; SE = 0.12 , $P < 0.0002$) (Table 4). The slope indicates a 0.5 ms shorter QTc in OC users compared to OC nonusers. When examined by OC generation, users of first and second generation progestins had a significantly shorter QTc than nonusers (first

generation: slope = -1.0 ms , SE = 0.18 , $P < 0.0001$; second generation: slope = -2.0 ms , SE = 0.23 , $P < 0.0001$) while third generation OC had no significant effect (slope = 0.6 ms , SE = 0.30 , $P = 0.051$) and users of fourth generation had a significantly longer QTc than nonusers (slope = 3.6 ms , SE = 0.35 , $P < 0.0001$) (Table 5).

When stratified by comorbidity and exposure to QTc-altering medications, a shorter QTc remained for all OCs combined compared to nonusers. This effect did not remain in patients with at least one comorbidity or in patients on other QTc-altering medications (Table 4). When examined by generation, a 4 ms longer QTc was observed with fourth generation OCs among women with no comorbidities and with no other prescriptions known to alter the QTc ($P < 0.001$) (Table 5). In women with one or more comorbidities, a more modest lengthening of the QTc by 2.8 ms was observed ($P < 0.0001$). There were no differences among the relatively small subgroup of women taking QTc-altering medications, with or without comorbidities.

DISCUSSION

These data examine, for the first time, OC use and QTc in a large integrated healthcare system population. Overall, OC users have a shorter QTc than nonusers. In addition, OC generation is an important predictor of QTc length after adjusting for age and comorbidity. First and second generation OC users with androgenic progestins have a shorter QTc while fourth generation OC users with antiandrogenic progestins have a longer QTc than nonusers. The effect of OC on the QTc was not modified by estrogen dose or contraceptive route of delivery.

Endogenous Sex Hormones and the QTc Interval

Observational studies support an association between testosterone and shorter QTc intervals.

Table 2. Characteristics of Women Ages 15–53 Years at Index ECG (N = 410,782)

	Women with no OC Prescription	Women with OC Prescription	P-Value
Number	376,106	34,676	
Age, years (mean ± SD)	40.7 ± 10.2	33.2 ± 9.6	<0.0001
Age categories, n (%)			<0.0001
15–20	23,841 (6.3)	4,016 (11.6)	
21–25	19,967 (5.3)	54,84 (15.8)	
26–30	27,669 (7.4)	6,038 (17.4)	
31–35	37,228 (9.9)	5,562 (16.0)	
36–40	51,075 (13.6)	4,926 (14.2)	
41–45	71,144 (18.9)	4,608 (13.3)	
46–50	87,987 (23.4)	3,346 (9.7)	
51–53	38,409 (10.2)	555 (1.6)	
Race, n (%)			<0.0001
White	154,193 (41.0)	16,462 (47.5)	
Black	35,516 (9.4)	2,263 (6.5)	
Asian & Pacific Islander	44,486 (11.8)	3,100 (8.9)	
Latino	55,911 (14.9)	4,907 (14.2)	
Native American	2,265 (0.6)	152 (0.4)	
Mixed	5,874 (1.6)	456 (1.3)	
Missing	77,861 (20.7)	7,336 (21.2)	
Number of ECGs (mean ± SD)	1.9 ± 2.1	1.6 ± 1.3	<0.0001
QTc at the index ECG, ms (mean ± SD)	403.5 ± 22.6	400.8 ± 21.3	<0.0001
Number of follow-up years (mean ± SD)	4.9 ± 3.6	4.5 ± 3.1	<0.0001
Smoking status, n (%)			<0.0001
Never	159,590 (42.4)	17,232 (49.7)	
Former	32,449 (8.6)	2,989 (8.6)	
Current	72,831 (19.4)	5,257 (15.2)	
Missing	111,236 (29.6)	9,198 (26.5)	
Comorbidities, n (%)			
Acute coronary syndrome	2,915 (0.8)	71 (0.2)	<0.0001
Cardiac arrest	261 (0.1)	6 (0.02)	0.0003
Transient ischemic attack	1790 (0.5)	67 (0.2)	<0.0001
Hemorrhagic stroke	613 (0.2)	18 (0.1)	<0.0001
Ischemic stroke	1782 (0.5)	47 (0.1)	<0.0001
Heart failure	2,857 (0.8)	84 (0.2)	<0.0001
Ventricular dysrhythmias	789 (0.2)	52 (0.2)	0.0184
Obesity	96,753 (25.7)	7,536 (21.7)	<0.0001
Hypertension	76,789 (20.4)	3,918 (11.3)	<0.0001
Diabetes	5,805 (1.5)	142 (0.4)	<0.0001
Hyperlipidemia	35,045 (9.3)	1,635 (4.7)	<0.0001
End-stage renal disease	1,138 (0.3)	30 (0.1)	<0.0001

ECG = electrocardiogram.

Specifically several studies have demonstrated that QTc intervals decrease with increasing tertiles of endogenous testosterone.^{7,12} Animal data support a QTc lengthening effect of endogenous estrogen. Specifically, Saito et al. compared the QTc of mice with high endogenous estrogen to ovariectomized mice with no detectable endogenous estrogen⁶ and found a significantly shorter QTc in the ovariectomized group (P < 0.05). In addition, when estradiol was added back to the ovariectomized group, the QTc lengthened to pre-surgical values. With regard to progesterone, data

on QTc alterations during the menstrual cycle support a shortening effect of progesterone on the QTc interval in women.^{4,5} Specifically, these studies report an inverse relationship between high progesterone levels and QTc length.

Hormone Therapy (HT) and QTc Interval

HT used in the peri- and postmenopause in terms of ET and EPT and the effects on the QT interval have been reported in numerous studies.^{2,3,13} These studies define ET as 0.625 mg/day of

Table 3. OC and QTc by Generation, Dose, and Route of Delivery

	Number of Women	QTc ± SD	P-Value*	P-Value**
OC generation				
First	15,719	400.8 ± 21.5	P < 0.0001	P < 0.0001
Second	9,303	399.2 ± 21.0		
Third	5,762	400.8 ± 21.1		
Fourth	3,890	403.5 ± 22.6		
Nonusers	376,106	403.5 ± 22.6		
OC dose				
Very low	571	402.0 ± 21.1	P < 0.0001	0.1866
Low	33,747	400.7 ± 21.3		
Moderate	157	402.7 ± 20.8		
Nonusers	376,106	403.5 ± 22.6		
Route				
Oral	34,118	400.7 ± 21.3	P < 0.0001	0.4942
Transdermal	360	401.3 ± 21.4		
Vaginal	198	402.4 ± 23.8		
Nonusers	376,106	403.5 ± 22.6		

OC = oral contraceptive use, QT_c = corrected QT.

*Includes women not on OC (OC nonusers) in analysis.

**Includes only women on OC in analysis.

Table 4. Effect of All OCs Combined on QTc Stratified by Comorbidity and Exposure to QTc-Altering Drugs

	n	Slope*	SE	P-Value
OC users vs. nonusers	410,782	-0.50	0.12	<0.0002
No comorbidities				
No drugs	240,745	-0.60	0.15	<0.0001
1 or more drugs	10,714	-1.14	0.61	0.06
1 or more comorbidities				
No drugs	143,788	-0.90	0.15	0.11
1 or more drugs	15,535	-1.28	0.44	0.65

*Relative to nonusers and adjusted for age, race/ethnicity and smoking status.

OC = oral contraceptive use, QT_c = corrected QT.

conjugated equine estrogen (CEE) and EPT as 0.625 mg/day of CEE plus 2.5 mg/day of medroxyprogesterone (MPA). Kadish et al. reported on 34,378 postmenopausal women participating in the dietary intervention component of the Women's Health Initiative.² They found that women on ET had significantly longer QTc intervals compared with women who were never treated with HT (P < 0.05). Women on EPT, in contrast, had no difference in QTc intervals compared with controls. These results were further supported by Carnethon et al. who studied 3,101 women from the Atherosclerosis Risk in Communities cohort.³ They reported that the likelihood of QTc prolongation in women on ET was nearly twice that compared to women never treated with HT (odds ratio = 1.9, 95% confidence interval: 1.2-2.0). EPT, in contrast, was not significantly associated with QTc length (odds ratio = 1.1, 95% confidence interval: 0.6-1.9). These studies

suggest a counterbalancing effect of exogenous oral estrogen and progesterone on the QTc.

Oral Contraception and QTc Interval

In general, OC uses doses of estrogen and progesterone that are 5-10 fold higher than that of HT. We report a small but significantly shorter QTc in OC users compared to nonusers. In addition, first and second generation OC shortened the QTc, while third generation OC had no effect and fourth generation OC lengthened the QTc by 4 ms in our large cohort. There were no significant differences in the QTc among the subgroup of women taking both 4th generation OCs and other QTc-altering medications. This is reassuring and suggests that the effects of the fourth generation OCs and other QTc-altering medications on the QTc may not be additive.

Table 5. Effect of OC Generation on QTc Stratified by Comorbidity and Exposure to QTc-Altering Drugs

	OC Generation*											
	1			2			3			4		
n	Slope (SE)	P-Value	Slope (SE)	P-Value	Slope (SE)	P-Value	Slope (SE)	P-Value	Slope (SE)	P-Value	Slope (SE)	P-Value
OC users by generation vs. nonusers	410,782	-1.0 (0.18)	<0.0001	-2.0 (0.23)	<0.0001	0.6 (0.30)	0.051	3.6 (0.35)	<0.0001			
No Comorbidities	240,745	-1.2 (0.28)	<0.0001	-2.2 (0.28)	<0.0001	0.5 (0.33)	0.15	4.0 (0.43)	<0.0001			
1 or more drugs	10,714	-1.0 (0.86)	0.23	-2.0 (0.11)	0.07	-2.4 (1.32)	0.07	2.0 (1.56)	0.19			
comorbidities	143,788	-0.8 (0.35)	0.02	-1.8 (0.47)	<0.0001	1.6 (0.68)	0.02	2.8 (0.71)	<0.0001			
No drugs	15,535	0.3 (0.94)	0.76	-2.2 (1.25)	0.07	1.3 (2.06)	0.52	0.2 (1.78)	0.90			

* Relative to nonusers and adjusted for age, race/ethnicity and smoking status. OC = oral contraceptive use, QTc = corrected QT.

Our results are concordant with the published endogenous hormone and HT data and support a counteracting effect of estrogen and progesterone on the QTc. In addition, similar to data on the QTc during the menstrual cycle, progesterone and more specifically the type of progestin in OCs appears to be the most important predictor of QTc length. Fourth generation OCs which contain antiandrogenic progestins lengthened the QTc and this is concordant with published data suggesting an overall QTc shortening effect of androgens.

One prior study has reported on the fourth generation OC Natazia (dienogest and estradiol valerate) which has just recently been approved by the FDA for the treatment of heavy menstrual bleeding in women who choose an oral contraceptive (OC) for contraception.¹⁴ This study was a double blind double-dummy placebo controlled crossover study of 3 mg of dienogest/2 mg estradiol valerate, 10 mg dienogest//2 mg estradiol valerate, placebo and moxifloxacin 400 mg in 53 subjects for 4 days per treatment. They showed no significant effect of Natazia on the QTc interval even at the higher dose, however there was only 4 days of exposure to the drug and small numbers of patients. Our study did not include Natazia as we studied subjects only until 2008. As such, perhaps the QTc lengthening effect we report is specific to drospiridone, the only fourth generation OC studied in our cohort.

Contraceptive Route of Delivery and QTc

With regard to hormonal contraception, routes of delivery such as transdermal and vaginal preparations, which avoid first pass metabolism in the liver, may provide a better safety profile.¹⁵ First pass metabolism of estrogen increases serum coagulation factors, triglycerides, and C-reactive protein and may lead to an imbalance between procoagulant factors and antithrombotic mechanisms.^{16,17,18} One study to date has examined the effects of transdermal HT on the QTc. Nowinski et al. randomized sixty postmenopausal women into 3 groups: oral CEE 0.625 mg/day for 18 days followed by 10 days combined with oral MPA 5 mg/day, transdermal 17-B-estradiol 50 ug/24 hours for 18 days followed by 10 days combined with oral MPA 5 mg/day, and transdermal placebo for 18 days followed by 10 days combined with oral

placebo tablets.¹⁹ QTc was measured at baseline, 6 and 12 months with no significant difference in QTc between the 3 different groups at any of these time intervals. Similarly, our current findings fail to demonstrate a significant difference in QTc between oral, vaginal, and transdermal preparations in terms of hormonal contraception. Unfortunately, we had small patient numbers in the vaginal and transdermal categories and our study is likely underpowered to detect differences. Future studies with larger numbers of patients on vaginal and transdermal hormonal contraception need to be performed before a definitive conclusion can be drawn.

Clinical Relevance of Longer QTc

It is well known that a prolonged QTc interval is a marker for an increased risk of ventricular tachyarrhythmias, specifically TdP and SCD¹ and prior studies have demonstrated that even a small increase in QTc is clinically relevant. Specifically, Noseworthy et al. in a large population based cohort in Finland demonstrated that a 10 ms increase in QTc corresponded with a 19% increase in SCD.²⁰ Strauss et al. in a prospective population based cohort study on men and women aged 55 years or older reported only a 10 ms difference between 6,009 controls (mean QTc = 431.3 ms) and 125 cases of SCD (mean QTc = 441.9 ms) ($P < 0.0001$).²¹ In addition, the Food and Drug Administration (FDA) considers potential risk when the QTc increases by >6–10 ms.

The fourth generation OCs currently approved for non-contraceptive indications, such as acne and premenstrual dysmorphic disorder, are in widespread use and have a relatively unknown cardiovascular safety record. Given that even a small prolongation in QTc appears to be clinically relevant, the 4 ms increase in QTc in fourth generation OC users that we observed is worrisome and warrants careful examination of adverse event rates in this population. In addition, while we did not find a significant additive effect of OCs with other QT prolonging drugs, it is still plausible that the addition of a fourth generation OC to common medications such as antibiotics and antihistamines, which are known to lengthen the QT by 5–10 ms, may increase the risk of sudden death.²²

Study Limitations

First, our study is cross-sectional and examined the QTc of the index ECG in OC users compared to OC nonusers. We were unable to follow the same patients before and after OC use as we did not have ECGs recorded before and after OC use in the database and therefore do not have time-dependent analyses. In addition, since patients were not prospectively randomized to OC versus no OC, it is possible that other inherent differences amongst patients who take OCs versus those that do not are responsible for the QTc differences observed. We did however attempt to correct for these inherent differences in our multivariate analysis and the effects of OC generation on QTc remained. Second, the ECGs used for this analysis were obtained in the course of the delivery of clinical care as part of diagnostic workups or preoperative protocols. These ECGs may not reflect a more generalized population than those whose ECGs were obtained as part of routine screening and annual physical examinations. In addition, only women with ECGs were included creating inherent bias. Third, we had small patient numbers in the vaginal and transdermal categories in addition to the very low and moderate estrogen dose categories, thus we may have been underpowered to detect a significant difference on the QTc. Fourth, the QTc difference we found was very small but perhaps still relevant as discussed above. Fifth, proof of health or lack of comorbidities was limited. Sixth, our software only allowed QT correction using log-linear regression and we were unable to verify our correction with other methods such as Fridericia's or Bazett's formulae.

CONCLUSION

Overall, OC users had a shorter QTc than nonusers. In addition, OC generation is an important predictor of QTc length after adjusting for age and comorbidity, with a shorter QTc seen with first and second generation OC. Fourth generation OC use with antiandrogenic progestins have a 4 ms longer QTc than first and second generation OC users. As even small QTc prolongation can be clinically relevant, careful examination of adverse event rates in fourth generation OC users is needed.

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Author Contributions: Drs. Sedlak, Bairey Merz, and Shufelt wrote the manuscript, performed the research and designed the research. Dr. Iribarren and Ms. Lyons performed the research and analyzed the data.

APPENDIX A

List of QTc prolonging drugs

Prescription	Therapeutic Class	Number of Patients
Isradipine	Antihypertensive	12
Nicardipine	Antihypertensive	9
Mexiletine	Antiarrhythmic	22
Solifenacin	Antispasmodic	6
Terbutaline	Bronchodilator	46
Dolasetron	Antinausea	152
Flecainide	Antiarrhythmic	209
Voriconazole	Antifungal	17
Chloral hydrate	Sedative/hypnotic	22
Gatifloxacin	Antibiotic	133
Sotalol	Beta blocker	371
Digoxin	Cardiac glycoside/anti-arrhythmic	3343
Tacrolimus	Immunosuppressant	200
Levetiracetam	Anticonvulsant	180
Haloperidol	Antipsychotic	449
Moxifloxacin	Antibiotic	960
Indapamide	Diuretic	222
Aripiprazole	Atypical antipsychotic	219
Galantamine	Psychoanaleptic/anti-dementia	29
Clozapine	Antipsychotic	52
Risperidone	Antipsychotic	980
Thioridazine	Antipsychotic	145
Protriptyline	Tricyclic antidepressant	34
Primidone	Anticonvulsant	245
Quetiapine	Antipsychotic	1006
Lidocaine	Local anesthetic/antiarrhythmic	512
Amiodarone	Antiarrhythmic	210
Atenolol	Beta blocker	29,347
Ondansetron	Antiemetic	464
Desipramine	Tricyclic antidepressant	411
Salmeterol	Long-acting β 2-adrenergic receptor agonist	2642
Atorvastatin	Lipid lowering/statin	1666
Carbamazepine	Anticonvulsant	1030
Ciprofloxacin	Antibiotic	3009
Levofloxacin	Antibiotic	195
Venlafaxine	Antidepressant/SSRI	2,047
Ofloxacin	Antibiotic	4099
Tolterodine	Antimuscarinic	563

(Continued)

Prescription	Therapeutic Class	Number of Patients
Midodrine	Antihypotensive	39
Levalbuterol	Short-acting beta agonist	32
Citalopram	Antidepressant/SSRI	2972
Diphenhydramine	Antihistaminic	165
Tizanidine	α -2 adrenergic agonist/Muscle relaxant	212
Vardenafil	Phosphodiesterase inhibitors	1622
Azithromycin	Antibiotic	1487
Albuterol	Short-acting β 2-adrenergic receptor agonist	8371
Chloroquine	Antimalaria	1105
Doxepin	Tricyclic antidepressant	804
Octreotide	Analogue of hypothalamic pituitary hormones	23
Nortriptyline	Tricyclic antidepressant	3816
Methadone	Opioid/antiaddictive	645
Chlorpromazine	Antipsychotic	67
Amitriptyline	Tricyclic antidepressant	3890
Sertraline	Antidepressant/SSRI	2589
Tamoxifen	Antineoplastic agent	1163
Fluconazole	Antifungal	629
Phenytoin	Anticonvulsant	1744
Phenylephrine	Decongestant	648
Paroxetine	Antidepressant/SSRI	6655
Amantadine	Antiviral	107
Atazanavir	Antiretroviral/protease inhibitor	61
Lamotrigine	Anticonvulsant	558
Clarithromycin	Antibiotic	206
Imipramine	Tricyclic antidepressant	1367
Lithium	Antidepressant/mood stabilizer	772
Atomoxetine	Psychostimulant for ADHD	95
Cotrimoxazole	Antibiotic	292
Fluoxetine	Antidepressant/SSRI	12,548
Sibutramine	Antiobesity/anorectic	63
Disopyramide	Antiarrhythmic	50
Procainamide	Antiarrhythmic	61
Pseudoephedrine	Decongestant	1946
Ephedrine	Decongestant	1998
Ketoconazole	Antifungal	355
Phentermine	Appetite suppressant	159
Quinidine	Antiarrhythmic	89
Epinephrine	Catecholamine/vasoconstrictor/inotropic	238
Erythromycin	Antibiotic	2157
Cisapride	GI tract promotility agent	141
Amphetamine	CNS stimulant	523
Itraconazole	Antifungal	43
Ziprasidone	Antipsychotic	314
Metaproterenol	Short-acting beta agonist	116
Pimozide	Antipsychotic	19
Methylphenidate	Psychostimulant (ADHD)	770
Fenfluramine	Appetite suppressant	31
Phenylpropanolamine	Decongestant/anorectic	323
Clomipramine	Tricyclic antidepressant	70
Trimipramine	Tricyclic antidepressant	19
Terfenadine	Antihistaminic	28

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