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Patterns of psychotropic medication prescribing and potential drug-hormone interactions among transgender and gender diverse adults within two years of hormone therapy

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Abstract

Background: Transgender and gender diverse (TGD) people have a high prevalence of psychotropic medication use, yet knowledge about the patient-level psychotropic medication burden is limited. TGD patients may take hormone therapy to meet their gender expression goals. Potential drug-hormone interactions exist between psychotropic medications and hormone therapy, requiring increased knowledge about psychotropic medication use for TGD adults undergoing hormone therapy.

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Objectives: To examine the extent of psychotropic medication polypharmacy in a cohort of TGD adults within two years of starting hormone therapy. We also characterized potential drug-hormone interactions and the association with psychotropic polypharmacy.

Methods: Retrospective cross-sectional analysis of patients with ≥1 transgender health-related visit (2007–2017) in the University of Washington Medical System (Seattle, WA). Eligible patients had ≥1 psychotropic medication including antidepressants, antipsychotics, mood stabilizers, and sedative-hypnotics ordered within two years of starting hormone therapy (testosterone or estradiol with or without spironolactone, progesterone, finasteride or dutasteride). We defined psychotropic polypharmacy as ≥2 psychotropic medication orders with overlapping treatment durations for at least 90 days and characterized potential drug-hormone interactions (Lexicomp, Hudson, OH). We descriptively summarized patients with and without polypharmacy (frequencies and percentages) and compared drug-hormone interactions using Chi-square or Fishers exact tests (P<0.05 considered significant).

Results: 184 patients had ≥1 psychotropic medication order within two years of hormone therapy; 68 patients (37.0%) had psychotropic polypharmacy. The most frequent type of psychotropic polypharmacy was antidepressant+sedative-hypnotic (18/68, 26.5%). More patients had a potential drug-hormone interaction among those with psychotropic polypharmacy (23/68, 33.8%) versus those without (8/116, 6.9%, P<0.001).

Conclusion: Among TGD patients on psychotropic medications within two years of hormone therapy, one-third had psychotropic polypharmacy. Most polypharmacy types appeared to align with mental health treatment guidelines. The number of patients with a potential drug-hormone interaction was significantly higher among those with polypharmacy. Prospective studies are needed to characterize drug-hormone interactions.

Keywords

mental health; psychotropic polypharmacy; transgender; hormone therapy; drug interactions

Background

More than one million people in the U.S. are transgender.[1] For transgender and gender diverse (TGD) people, gender-affirming medical care includes psychological support, hormone therapy, and surgical interventions that people may undergo to support their gender expression goals.[2] Because TGD people may take medication therapies for both hormone therapy and mental health care,[3, 4] increased knowledge about patterns of medication use is needed to identify and manage medication therapy-related problems for TGD people.

TGD people experience substantial psychosocial stigma and discrimination. Investigators have noted a high prevalence of depression and anxiety among TGD people,[2] and social stigma was positively associated with depression, anxiety, and somatization for more than 1,000 U.S. transgender adults in an Internet-based analysis.[5] Emerging data suggest a high prevalence of psychotropic medication use among TGD people worldwide.[6, 7] An analysis of the 2005–2015 Swedish Total Population and Prescribed Drug Registers observed TGD adults (average age 31.5 years) had nearly four times higher odds of being prescribed either an antidepressant or an anxiolytic medication compared with the general adult population

(average age 40.7 years).[7] Among adults receiving Medicare benefits due to a disability between 2009–2014, investigators observed numerically higher psychotropic medication use among gender minority beneficiaries relative to other beneficiaries (71% vs. 49%).[6] More than half of psychiatric visits in 2014–2015 among the general U.S. adult population with depression included prescriptions for two or more psychotropic medications,[8] but the patient-level psychotropic medication burden for TGD people has yet to be determined.

Using two or more psychotropic medications from multiple medication classes may lead to drug-drug interactions.[9] Although drug-drug interaction studies inclusive of TGD people are limited, potential drug-hormone interactions may occur between gender-affirming hormone therapies and psychotropic medications.[4, 10–12] As one example, TGD people may take 17β-estradiol for feminization.[3] A case-control analysis observed 17β-estradiol (as menopausal hormone therapy) was associated with low serum concentrations of lamotrigine, a second-generation antiseizure medication FDA-approved for maintenance treatment of mood episodes in bipolar I disorder.[12] The clinical implications of this drug-hormone interaction for TGD people with mood disorders remain to be determined, and increased knowledge about psychotropic medication use among TGD people is needed.

Objective(s)

Our primary objective was to examine the patient-level psychotropic medication burden among TGD adult patients within two years of starting hormone therapy in a real-world clinical setting. Our secondary objective was to investigate medication therapy-related problems (i.e., potential drug-hormone interactions) for TGD patients prescribed more than one psychotropic medication. We hypothesized many TGD patients would have two or more psychotropic medication orders (psychotropic polypharmacy) within two years of starting hormone therapy and that most potential drug-hormone interactions would occur among those patients with psychotropic polypharmacy.

Methods

Study design and patient sample

We conducted a single-system, multicenter, retrospective cross-sectional analysis of electronic medical records within the University of Washington (UW) Medicine Electronic Data Warehouse, a centralized electronic medical record repository of data across University of Washington Medicine inpatient and outpatient clinics.[13] UW Medicine is an integrated health system that provides gender-affirming medical care for TGD people in primary care and specialty care settings. We identified patients aged ≥18 years with at least one transgender health-related clinical visit in the University of Washington Medicine system between 2007–2017 (Table S1).[13–15] Eligible patients had at least 3 months of continuous orders for 17β-estradiol or testosterone (index date = first hormone therapy order date), limiting our sample to patients who started and were maintained on hormone therapy.[13] Because gender identity and expression data are often incompletely collected and recorded in the electronic health record,[16] we grouped patients based on whether they had medication orders for estrogen or testosterone treatment over our study period.[13] We followed the Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) guidelines to prepare our manuscript.[17] The University of Washington Institutional Review Board reviewed this analysis.

Measures

We extracted demographic characteristics, hormone therapy-related medication orders, psychotropic medication orders, medication order start and end dates, and psychiatric and co-occurring diagnoses using International Classification of Diseases (ICD) Ninth or Tenth Revision diagnosis codes (Table S1).[8, 14, 15, 18–20] We used the term “medication orders” for consistency throughout the text to characterize all medication requests, including those sent to both inpatient and outpatient dispensers.

Psychotropic medication prescribing and polypharmacy

We determined the number of patients with at least one medication order for an antidepressant, antipsychotic, mood stabilizer, sedative-hypnotic, anxiolytic, stimulant, medication for alcohol and opioid use disorder, or medications with off-label psychiatric indications (e.g., oxcarbazepine, prazosin) and included medications FDA approved before and during our study period (Table S2).[8, 18]

We determined the number of patients with two or more antidepressant, antipsychotic, mood stabilizer, and sedative-hypnotic medication orders for at least 90 days of concurrent therapy (psychotropic medication polypharmacy) (Table S2).[8, 18, 21, 22] We characterized the polypharmacy type as either between-class (two or more medication classes) or within-class (one medication class). We examined and excluded medications from our analysis if they were associated with a non-psychiatric-related diagnosis in the electronic health record (Tables S1, S2).[8, 14, 15, 18–20] These medications included carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproate/divalproex, phenobarbital, gabapentin, and pregabalin (epilepsy, convulsions); clonidine, guanfacine, prazosin and beta-blockers (hypertensive diseases; benign prostatic hyperplasia or Raynaud’s syndrome [prazosin only]); and selegiline, benztropine, and trihexyphenidyl (Parkinson’s disease).[8, 18] Because TGD people have a high prevalence of nicotine use disorder,[19] and bupropion is FDA-approved for both major depressive disorders and smoking cessation, we summarized the number of patients with a bupropion order and an associated tobacco use diagnosis (Table S1).[20]

Evaluation of potential drug-drug interactions between psychotropic medications and hormone therapies

We identified the following medications based on expert recommendations for gender-affirming hormone therapy in U.S. clinic settings: estradiol or testosterone, spironolactone, progesterone, finasteride or dutasteride.[23] We examined potential interactions between hormone therapies and psychotropic medications using the Lexicomp® Drug Interactions online application (Hudson, OH) with any risk rating (A - no known interaction, B - no action needed, C - monitor therapy, D - consider therapy modification, X - avoid combination).[24, 25] Because hormone therapies are prescribed off-label for gender-affirming hormone therapy, we excluded drug-drug interactions unlikely to be clinically relevant for gender-affirming medical care (e.g., the antagonistic effects of stimulants on

the blood pressure-lowering effect of spironolactone). Because we focused on drug-hormone interactions, we summarized drug-drug interactions between psychotropic medications with risk ratings D or X only.

Data analysis

We used descriptive statistics (frequency and percent) to summarize sample characteristics. We compared categorical data using Chi-square or Fisher exact tests and continuous data using the Wilcoxon rank sum test based on the non-normality of the result distribution. A P value <0.05 was considered statistically significant (SAS software, v9.2, SAS Institute, Inc., Cary, NC).

Results

Patient sample and frequency of psychotropic medication orders

One-hundred eighty-four TGD patients (of 349 patients, 52.7%) had at least one psychotropic medication order within two years of hormone therapy (Figure S1). Demographic characteristics were similar between patients with and without a psychotropic medication order (data not shown), although the number of patients with a psychiatric diagnosis was higher among those with at least one psychotropic medication order (93.5% vs. 31.5%, P<0.001). Among 184 patients with at least one psychotropic medication order, the median follow-up duration was 430 days post-index date (interquartile range: 307–569 days). A plurality had an order for either an anxiolytic medication (such as alprazolam, buspirone, chlordiazepoxide, clonazepam, diazepam, diphenhydramine, hydroxyzine, lorazepam, or propranolol, 91/184, 49.5%), a selective serotonin reuptake inhibitor (75/184, 40.8%), or a miscellaneous antidepressant such as bupropion, nefazodone, or trazodone (64/184, 34.8%) (Table 1). Of 39 patients with a bupropion order, 11 patients had an associated tobacco use diagnosis.

Patterns of psychotropic polypharmacy

Sixty-eight patients (68/184, 37.0%) met our definition of psychotropic medication polypharmacy. The number of patients with psychiatric and co-occurring diagnoses was significantly higher among those with polypharmacy versus without (P=0.004). A significantly higher number of patients with polypharmacy had an order for at least one of the following medication classes: anxiolytic, miscellaneous antidepressants, antipsychotics, mood-stabilizers, sedative-hypnotics, adrenergic agents, and serotonin-norepinephrine reuptake inhibitors (Table 1). The type and number of hormone therapies ordered for patients with versus without polypharmacy were similar (Table 1).

Fifty-two patients had between-class polypharmacy and 46 patients had within-class polypharmacy. The most frequent (>15%) between-class polypharmacy types were antidepressant + sedative-hypnotic (18/68, 26.5% patients) and antidepressant + antipsychotic (13/68, 19.1% patients). The most frequent within-class polypharmacy types were antidepressants (30/68, 44.1% patients) and sedative-hypnotics (14/68, 20.6% patients) (Table 2).

Potential drug-hormone interactions and association with psychotropic polypharmacy

Thirty-one patients (of 184, 16.8%) had at least one overlapping combination of psychotropic medications and hormone therapies with a potential drug-hormone interaction (Figure S2). More patients had a potential drug-hormone interaction among those with psychotropic polypharmacy (23/68, 33.8%) versus those without psychotropic polypharmacy (8/116, 6.9%, $P<0.001$). We identified 10 types of potential drug-hormone interactions total, all of which were a risk rating C ("monitor therapy").[24] Most drug-hormone interactions were related to additive blood pressure-lowering effects of spironolactone with antipsychotic, antidepressant, or adrenergic medications (29/31 patients, 93.5%). The remaining drug-hormone interactions were pharmacokinetic in nature and included lamotrigine plus estradiol (4/31 patients: potentially decreased lamotrigine concentration), lithium plus spironolactone (3/31 patients: potentially increased lithium concentration) and alprazolam plus spironolactone (2/31 patients: potentially increased alprazolam concentration) (Figure S2). We observed no category D or X drug-drug interactions between psychotropic medications.

Discussion

Most TGD patients (≥50%) had at least one psychotropic medication order within two years of starting hormone therapy. Of these patients, 37% met our definition of psychotropic polypharmacy. To our knowledge, this is the first analysis of psychotropic medication polypharmacy in a cohort of TGD patients undergoing hormone therapy.

For patients with two or more overlapping psychotropic medication orders, the most frequent psychotropic combinations were antidepressant plus sedative-hypnotic and antidepressant plus antipsychotic. Mental health care providers may use adjunctive treatments (i.e., adding a second medication to an initial medication) to manage treatment-resistant depression and bipolar disorder.[26, 27] Updated treatment guidelines for depression also highlight combined use of certain psychotropic agents, including atypical antipsychotics with antidepressants.[28] Although we were unable examine the clinical rationale for the polypharmacy types in our analysis, based on the medication combinations observed, our findings provide reassurance that instances of psychotropic polypharmacy may have been aligned with current standards for clinical care.

The number of patients with a potential drug-hormone interaction was significantly higher among patients with psychotropic polypharmacy. Among all 31 patients with a potential drug-hormone interaction, most were related to the additive hypotensive effects of spironolactone and second-generation antipsychotic medications. Spironolactone, a potassium-sparing diuretic, is an antiandrogenic agent typically in addition to estrogen treatment for gender care.[3, 23] Second-generation antipsychotics olanzapine, quetiapine, and risperidone are associated with orthostatic hypotension,[29, 30] with two times higher odds of orthostatic hypotension relative to placebo in randomized controlled trials.[31] To our knowledge, no case reports characterize additive hypotensive effects of spironolactone plus psychotropic medications. Further investigation of this drug-drug interaction, particularly among older TGD adults, is warranted.

Few patients (4 patients total) had medication orders for estradiol plus lamotrigine. Although speculative, this low number may reflect prescribers' avoidance of this combination due to its established drug-drug interaction. The magnitude of this interaction can diminish seizure control for patients living with epilepsy, but the effects of this pharmacokinetic interaction on mood disorders remains to be determined. For TGD people taking lamotrigine for mood symptoms, experts have recommended identifying and maintaining pre-estrogen treatment serum lamotrigine concentrations if these concentrations were effective for management before hormone therapy.[32]

Because of overlapping metabolic pathways of hormone therapies and psychotropic medications,[4] other pharmacokinetic drug-hormone interactions may occur outside of those identified in our cohort.[10] For example, several cytochrome P450 (CYP) enzymes metabolize 17β-estradiol and testosterone, including CYP3A, CYP2B6, and CYP2C9.[33] Carbamazepine, an antiseizure medication used as a mood stabilizer, causes broad spectrum CYP induction that may decrease estradiol or testosterone concentrations.[4] Conversely, the antidepressant nefazodone, a CYP3A4 inhibitor, could increase serum estradiol or testosterone concentration.[4] Reassuringly, no patients in our cohort had medication orders for these medication combinations. Our investigation of testosterone-related drug-hormone interactions was hampered by limited clinical drug interaction data for testosterone treatment for any patient population. Prospective pharmacokinetic studies to characterize and address drug-hormone interactions for TGD patients are warranted.

Our single system, multicenter design allowed us to characterize psychotropic medication prescribing across clinics within the University of Washington Medical System. However, this hypothesis-generating analysis had certain limitations. We based our definition and analysis of polypharmacy on previous studies of psychotropic polypharmacy,[8, 21, 22] and we acknowledge experts may define polypharmacy differently across clinical settings and patient populations.[34] Because we followed previously defined methods for our analysis of psychotropic polypharmacy,[8, 18] and these methods excluded certain medication classes including stimulants and anxiolytics not otherwise characterized as sedative-hypnotics, we may have underestimated the extent of polypharmacy within our cohort.

We did not directly assess patients' adherence to psychotropic medications or hormone therapies, and we were unable to assess the clinical outcomes related to potential drug-hormone interactions. We used convenience sampling for our study sample, which may have introduced selection bias limiting the generalizability of our findings to TGD patients within the University of Washington Medical System only. Not every TGD person either wants or has access to medical care or hormone therapy. Further, hormone therapies are individualized and may include a combination of both testosterone and estrogen therapies, use of adjunctive agents alone (e.g., spironolactone), or low-doses of estradiol or testosterone.[23] Our approach to grouping hormone therapies in this analysis was not intended to oversimplify the diversity of gender expression or medical interventions for TGD people.

Prospective pharmacokinetic studies are needed to characterize the effects of diverse hormone therapy regimens on the magnitude of potential drug-hormone interactions.

Because most of our cohort was between ages 18–45 years, a separate analysis is necessary to estimate psychotropic polypharmacy for older TGD adults. Although outside the scope of this analysis, future studies should characterize neuropathic pain, functional gastrointestinal disorders, and the extent of off-label psychotropic medication prescribing for these conditions for TGD people.[35, 36]

Conclusion

Among TGD patients with least one psychotropic medication order within two years of hormone therapy, more than one third met our definition of psychotropic polypharmacy. The number of patients with potential drug-hormone interactions was significantly higher among those with psychotropic polypharmacy than without. Most potential drug-hormone interactions were related to additive pharmacodynamic effects of spironolactone with second-generation antipsychotics. Pharmacists must understand and manage potential drug-hormone interactions between hormone therapy and psychotropic medications to support drug safety and efficacy of both medication classes for TGD people.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What was already known

- Transgender and gender diverse (TGD) people experience high rates of stigma and discrimination, which may be linked with a high prevalence of depression and anxiety for this population. Recent population-based analyses observed a high prevalence of psychotropic medication use among TGD people worldwide.
- In mental health care settings, two or more psychotropic medication may be used as a strategy to manage certain conditions like treatment-resistant depression. Use of multiple medications may contribute to increased risk of drug-drug interactions. The patient-level medication burden for TGD people taking psychotropic medications remains to be determined.
- Gender-affirming medical care is associated with increased quality of life for TGD people may include hormone therapies. Clinically significant drug-drug interactions exist between certain hormone therapies and psychotropic medications.

What this study adds

- 184 TGD patients had at least one psychotropic medication order within two years of starting estrogen or testosterone treatment.
- Of these patients, more than one-third had two or more psychotropic medications with overlapping treatment durations (psychotropic medication polypharmacy). Most types of psychotropic polypharmacy appeared to align with current mental health treatment guidelines.
- The number of TGD patients with a potential drug-hormone interaction was significantly higher among those with psychotropic polypharmacy versus those without. Most were potential drug-hormone interactions related to additive hypotensive effects of spironolactone plus second generation antipsychotics.

Table 1.

Demographic characteristics among transgender and gender diverse patients within two years of hormone therapy with and without psychotropic polypharmacy in the University of Washington Medical System (2007–2017).[a]

Characteristic	Polypharmacy, N=68	No polypharmacy, N=116	*P* value
Ages, years			
18–44	50 (73.5)	84 (72.4)	0.9
45–64	16 (23.5)	31 (26.7)	0.6
65+	2 (2.9)	1 (0.9)	0.6
Race/ethnicity			
White	34 (50.0)	84 (72.4)	**0.002**
Black	6 (8.8)	8 (6.9)	0.6
Hispanic or Latino	6 (8.8)	8 (6.9)	0.6
American Indian or Alaska Native	3 (4.4)	3 (2.6)	0.7
Asian, Pacific Islander	4 (5.9)	6 (6.9)	1.0
Unknown	4 (5.9)	7 (6.0)	1.0
Hormone therapy			
Estrogen group	44 (64.7)	72 (62.1)	0.7
Testosterone group	24 (35.2)	44 (37.9)	-
Estradiol or testosterone alone	29 (42.6)	57 (49.1)	0.4
Combination (estradiol or testosterone plus one or more adjunctive hormone therapies)[b]	39 (57.4)	59 (50.9)	-
Psychiatric and co-occurring diagnoses	68 (100)	104 (89.7)	**0.004**
Major depression	59 (86.8)	74 (63.8)	**<0.001**
Anxiety disorders[c]	55 (80.9)	64 (55.2)	**<0.001**
Insomnia	30 (44.1)	27 (23.3)	**0.003**
Substance use disorder[d]	23 (33.8)	32 (27.6)	0.4
Other affective disorders	18 (26.5)	9 (7.8)	**<0.001**
Bipolar disorder	16 (23.5)	7 (6.0)	**<0.001**
Posttraumatic stress disorder	16 (23.5)	13 (11.2)	**0.03**
Schizophrenia	8 (11.8)	5 (4.3)	0.06
ADHD	7 (10.3)	17 (14.7)	0.4
Autism spectrum disorder	5 (7.4)	2 (1.7)	0.1

Characteristic	Polypharmacy, N=68	No polypharmacy, N=116	*P* value
Total psychotropic medications per patient	4.0 (3.0–6.0)	1.0 (1.0–2.0)	**<0.001**
Psychotropic medication classes			
Anxiolytic[e]	50 (73.5)	41 (35.3)	**<0.001**
Miscellaneous antidepressant[f]	37 (54.4)	27 (23.3)	**<0.001**
SSRI	32 (47.1)	43 (37.1)	0.2
Antipsychotic	33 (48.5)	15 (12.9)	**<0.001**
Mood stabilizer	28 (41.2)	23 (19.8)	**0.002**
Sedative-hypnotic	16 (23.5)	8 (6.9)	**0.001**
Adrenergic agent[g]	13 (19.1)	4 (3.4)	**<0.001**
SNRI	12 (17.6)	8 (6.9)	**0.02**
TCA	10 (14.7)	8 (6.9)	0.1
Tetracyclic	6 (8.8)	5 (4.3)	0.2
Stimulant	5 (7.4)	10 (8.6)	0.8
MAOI	0	0	-
Psychotropic polypharmacy[h]			
Between-class	52 (76.5)	-	
Within-class	46 (67.6)	-	

Data presented as counts and percentages or medians and interquartile ranges, as appropriate. Between group frequency data were compared using either Chi-square or Fisher exact tests, as appropriate. Continuous data compared with Wilcoxon rank sum test. **Bold** text indicates $P<0.05$.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; MAOI, monoamine oxidase inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

[a] We defined psychotropic polypharmacy as at least two antidepressant, antipsychotic, mood-stabilizer, or sedative-hypnotic orders with overlapping treatment durations for at least 90 days (continuous).

[b] Adjunctive hormone therapies include spironolactone, progesterone, finasteride or dutasteride.

[c] Included generalized anxiety disorder, panic disorder with or without agoraphobia, and obsessive-compulsive disorder.

[d] Includes alcohol use disorder, tobacco use disorder, and opioid use disorder.

[e] alprazolam, buspirone, chlordiazepoxide, clonazepam, diazepam, diphenhydramine, hydroxyzine, lorazepam, propranolol. Note: some medications may also be used as a sedative-hypnotic.

[f] bupropion, nefazodone, trazodone.

[g] clonidine, prazosin.

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[h] Because certain patients may have had within-class and between-class psychotropic polypharmacy, both groups combined are >100% of the cohort.

Table 2.

Frequency of between-class and within-class psychotropic polypharmacy medication types, N=68

Between-class medication combinations (N=52)
Antidepressant + Sedative-hypnotic (18)
Antidepressant + Antipsychotic (13)
Antipsychotic + Sedative-hypnotic (5)
Antidepressant + Antipsychotic + Sedative-hypnotic (5)
Antidepressant + Antipsychotic + Mood-stabilizer (4)
Antipsychotic + Mood stabilizer + Sedative-hypnotic (2)
Antidepressant + Antipsychotic + Mood Stabilizer + Sedative-hypnotic (3)
Antidepressant + Mood-stabilizer + Sedative-hypnotic (1)
Mood-stabilizer + Sedative-hypnotic (1)
Within-class medication combinations (N=46)[a,b]
Antidepressant (30)
Sedative-hypnotic (14)
Antipsychotic (5)
Mood-stabilizer (2)

[a]Total includes 30 patients with both within-class and between-class polypharmacy; these patients were also counted in the between-class polypharmacy list above.

[b]Because some patients had within-class polypharmacy for 2 or more medication classes, the total number of medication combinations per patient is >100% the number of individual patients.