JPPT | Single Multistate Health Care System Retrospective Study

Opportunities for Pharmacogenomics in Pediatrics: Prescribing Trends of Psychiatric Medications With Pharmacogenomic Implications at a Multistate Pediatric Health System

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The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines providing pharmacogenomic (PGx) recommendations for more than 100 drugs; however, limited data exist describing prescribing patterns of these medications in pediatric populations. With increasing evidence describing the benefits of PGx testing to tailor drug therapy in psychiatric conditions, along with a worsening mental health crisis in pediatrics, it is vital to assess the prevalence of medication prescribing and potential impact of implementing PGx testing in this population. Here we describe prescribing patterns of psychiatric drugs classified as CPIC level A/B from January 1, 2010, through December 31, 2020, across Nemours Children's Health, a multistate pediatric health care system. We identified 21,442 unique patients who received at least 1 indicated medication during this period. The most frequently prescribed medications were amitriptyline and sertraline. Overall prescribing was highest in the departments of neurology, primary care, and psychiatry with selective serotonin reuptake inhibitors (SSRIs) being the most frequently prescribed medication class. These findings indicate ample opportunity for PGx implementation targeting these medications. Identification of high-prescribing departments and specific medications prescribed will help focus PGx implementation and education efforts.

ABBREVIATIONS ADHD, attention-deficit/hyperactivity disorder; CPIC, Clinical Pharmacogenetics Implementation Consortium; NCH, Nemours Children's Health; PGx, pharmacogenomic; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant

KEYWORDS medication use evaluation; mental health; pediatric; pharmacogenetics; pharmacogenomics; primary care; psychiatry; selective serotonin reuptake inhibitors

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Introduction

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines providing pharmacogenomic (PGx) recommendations for more than 100 drugs[1]; however, limited data exist describing prescribing patterns of these medications in pediatric populations.[2] With increasing evidence describing the benefits of PGx testing to tailor drug therapy in psychiatric conditions,[3] along with a worsening mental health crisis in pediatrics,[4] it is vital to assess the prevalence of medication prescribing and potential impact of implementing PGx testing in this population. In this study, we describe the prescribing patterns of psychiatric medications with PGx implications over the past decade across Nemours Children's Health (NCH), a multistate pediatric health care system.

Methods

Prescription data for psychiatric drugs classified as CPIC level A/B[5] (Table 1, based on CPIC classifications as of August 1, 2023), hereinafter referred to as "PGx psych" medications, were extracted from the PEDSnet database[6] for all NCH locations from January 1, 2010, through December 31, 2020. These data included medication name, dose, route, frequency, date prescribed, prescribing provider specialty/department, site, and patient demographics. Only the first prescription for each unique drug per patient was included, unless otherwise specified. For prescribing by gene, patients were counted as based on the first prescription for each unique gene. For PGx psych medication prescribing by department, patients were counted as based on the first prescription for each unique patient prescribed by each department, therefore patients could be counted

Table 1. Patient Demographics*

Demographic	Number of Unique Patients (%) N = 21,442
Sex	
Female	11,503 (53.6)
Male	9939 (46.4)
Race†	
White or Caucasian	15,163 (70.7)
Black or African American	2808 (13.1)
Some other race	1912 (8.9)
Unknown	848 (4.0)
Multiracial	449 (2.1)
Asian	204 (1.0)
American Indian or Alaska Native	32 (0.2)
Hawaiian Native or Other Pacific Islander	26 (0.2)
Ethnicity	
Non-Hispanic or Latino	18,617 (86.8)
Another Hispanic, Latino, or Spanish origin	1953 (9.1)
Unknown	527 (2.5)
Puerto Rican	228 (1.1)
Mexican, Mexican American, Chicano/a	96 (0.5)
Cuban	21 (0.1)
Age at first medication, median (IQR), yr‡	14 (6)
Age at first medication prescribed by age category‡	
<1 yr	38 (0.2)
1–7 yr	2076 (9.7)
8–14 yr	8366 (39.0)
15–21 yr	10,962 (51.1)
Total number of unique medications per patient	
1	17,726 (82.7)
2	2901 (13.5)
3	656 (3.1)
≥4	159 (0.7)
Patients prescribed medication associated with each gene§	
CYP2C19	15,680 (73.1)
CYP2D6	14,032 (65.4)
CYP2B6	6044 (28.2)
HLA-A/HLA-B/SCN1A	439 (2.0)
NCH site	
Delaware	12,318 (57.4)
Jacksonville	4387 (20.5)
Orlando	4303 (20.1)
Pensacola	434 (2.0)

NCH, Nemours Children's Health

* All data reported as number (%), unless otherwise specified. Numbers may not add to 100% owing to rounding.

† Asian includes Asian, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, and Other Asian. Hawaiian Native or Other Pacific Islander includes Guamanian or Chamorro, Native Hawaiian, and Other Pacific Islander. Multiracial includes any persons who selected more than 1 race, unless the selected multiple races were already collapsed into the same category. Race was self-reported with the following options: American Indian or Alaska Native, Asian, Asian Indian, Black or African American, Chinese, Filipino, Guamanian or Chamorro, Hawaiian Native or Other Pacific Islander, Japanese, Korean, Native Hawaiian, Other Asian, Other Pacific Islander, Refused, Samoan, some other race, Vietnamese, White or Caucasian.

‡ For 2011–2020 to target new start medications; n = 20,408.

§ Numbers do not add to 100% because some patients were prescribed medications associated with more than 1 gene.

for more than 1 department. Drugs with genetic implications related to specific disorders (i.e., valproic acid, divalproex sodium), orders for topical administration, and patients older than 21 years were excluded. All data were analyzed in $R_{4.3.0}$ or GraphPad $Prism_{9.4.1}$. Descriptive statistics were used as appropriate. Year-over-year

changes in prescribing patterns were calculated by using Supplemental Equation S1.

Results

A total of 21,442 unique patients received at least 1 PGx psych medication between 2010 and 2020 across NCH (Table 1). The number of unique PGx psych medications prescribed for each patient was 1 (n = 17,726; 82.7%), 2 (n = 2901; 13.5%), 3 (n = 656; 3.1%), and 4 or more (n = 159; 0.7%). The most frequently prescribed medications were amitriptyline and sertraline (Table 2). Overall prescribing was highest in the departments of neurology, primary care, and psychiatry (Figure A and B; Supplemental Tables S1 and S2).

To assess the prescribing of new PGx psych medications across the study period, we selected unique first prescriptions for all included medications for each patient from 2011–2020 (Supplemental Table S3). The most frequently prescribed medications by class were selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs); serotonin-norepinephrine reuptake inhibitors (SNRIs) and anticonvulsants were infrequently prescribed (Figure C). SSRI and TCA prescriptions demonstrated a 10-year increase of 142.3% and 43.7%, respectively. Medications prescribed to treat attention-deficit/hyperactivity disorder (ADHD), antipsychotics, and SNRIs demonstrated no significant change in prescribing over time, while anticonvulsants demonstrated a decrease in prescribing rates over time.

Given the increase in SSRI prescriptions, we further explored their prevalence over the study period (Supplemental Table S4). The most frequently prescribed SSRIs included sertraline, escitalopram, and citalopram (Figure D). Over time, escitalopram and sertraline demonstrated the greatest increase in prescription of 319.5% and 212.4%, respectively. Citalopram prescriptions were notably reduced over time with a 10-year decrease in prescribing of 66.7%. As the total number of SSRI prescriptions increased over time by 142.3%, we also reviewed the share of each SSRI relative to the total number of SSRIs prescribed (Figure E). Relative prescribing of both escitalopram and sertraline increased from 20.0% to 34.7% and 46.1% to 59.5%, respectively. Citalopram prescriptions declined from 28.3% to 3.9%. From 2017 onward, escitalopram and sertraline made up >88% of all newly prescribed SSRIs.

Table 2. PGx Psych Medication Prescribing by Unique Patient 2010–2020

Drug Name	Gene(s)	CPIC Rating	Number of Unique Patients (%) N = 21,442
Amitriptyline*	*CYP2C19* *CYP2D6*	A A	6480 (30.2)
Sertraline*	*CYP2B6* *CYP2C19*	B A	6044 (28.2)
Escitalopram*	*CYP2C19*	A	2896 (13.5)
Risperidone	*CYP2D6*	B	2763 (12.9)
Atomoxetine*	*CYP2D6*	A	2363 (11.0)
Aripiprazole	*CYP2D6*	B	2250 (10.5)
Citalopram*	*CYP2C19*	A	1310 (6.1)
Nortriptyline*	*CYP2D6*	A	575 (2.67)
Carbamazepine*	*HLA-A* *HLA-B* *SCN1A*	A A B	439 (2.1)
Imipramine*	*CYP2C19* *CYP2D6*	B B	305 (1.4)
Fluvoxamine*	*CYP2D6*	B	198 (0.9)
Paroxetine*	*CYP2D6*	A	181 (0.8)
Doxepin*	*CYP2C19* *CYP2D6*	B B	123 (0.6)
Venlafaxine*	*CYP2D6*	B	113 (0.5)
Pimozide	*CYP2D6*	A/B	82 (0.4)
Clomipramine*	*CYP2C19* *CYP2D6*	B B	33 (0.2)
Vortioxetine*	*CYP2D6*	A	8 (0.04)
Desipramine*	*CYP2D6*	B	7 (0.03)
Trimipramine*	*CYP2C19* *CYP2D6*	B B	0 (0)

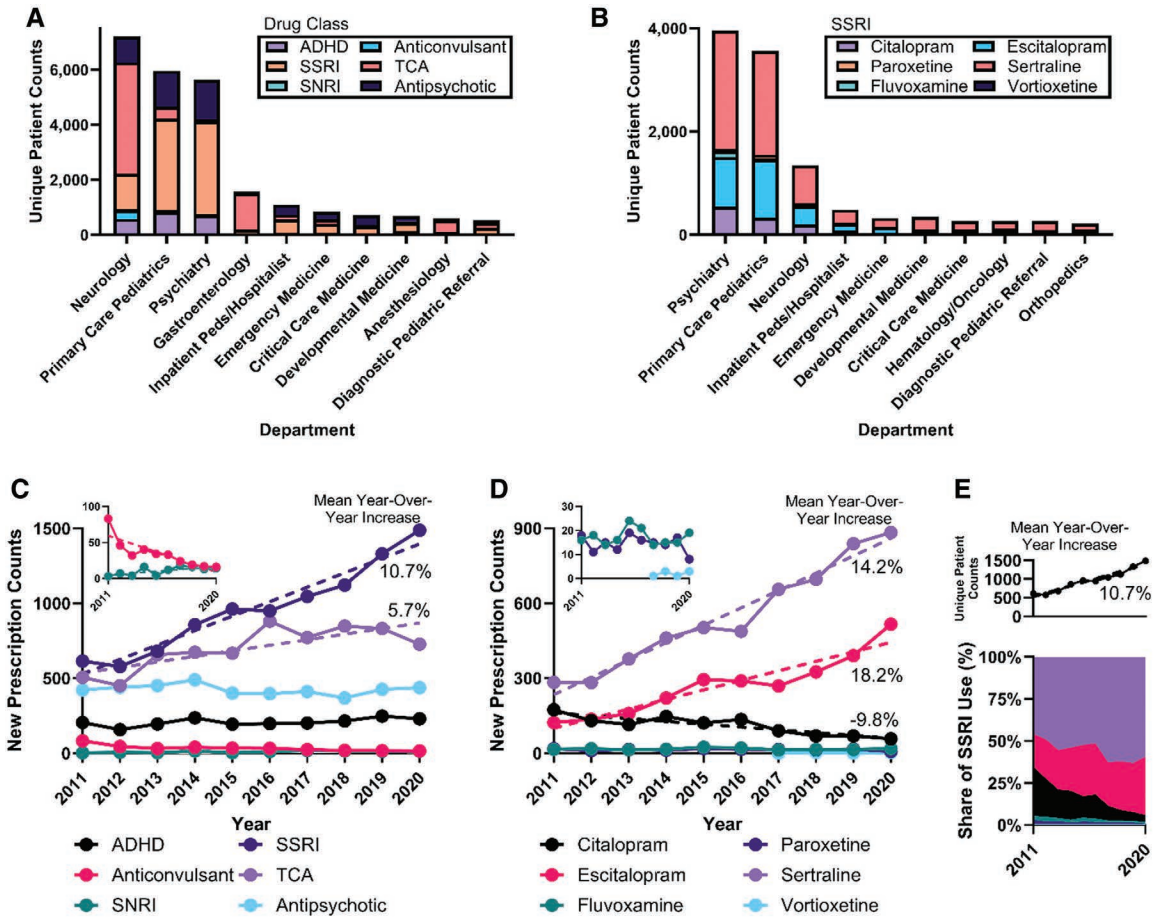
CPIC, Clinical Pharmacogenetics Implementation Consortium; PGx Psych, psychiatric drugs classified as CPIC level A/B

*CPIC guideline available.

Discussion

Across a large multicenter pediatric cohort, we found increasing use of psychiatric medications that could be guided by PGx data. Identification of high-prescribing departments and specific medications prescribed will help focus PGx implementation and education efforts.[7] Previous reports suggest certain SSRIs, notably citalopram and escitalopram, are some of the most commonly prescribed CPIC level A medications for pediatric patients.[8] We found SSRIs to be among the most frequently prescribed medications in this cohort; however, the most frequently prescribed SSRIs here were sertraline and escitalopram. This difference is likely due to the recent inclusion of sertraline to CPIC level A and exclusion of sertraline from prior studies.[7] While some previous studies only examine CPIC level A medications, we chose to include medications with CPIC level B ratings because these medications have at least 1 recommendation for change in prescribing based on genetics.[5] While

Figure. PGx psych medication prescribing by department and year. (A) Unique PGx psych medication prescriptions over the study period categorized by the top 10 prescribing departments and drug class. (B) Unique PGx psych medication prescriptions for SSRIs, the most highly prescribed PGx medication class in this cohort, over the study period, categorized by the top 10 prescribing departments and individual drug. (C) First-time prescriptions for PGx psych medication for unique individual patients from 2011 through 2020 demonstrated an increase in the use of SSRIs and TCAs, with a mean year-over-year increase of 10.7% and 5.7%, respectively. Anticonvulsants and SNRIs were infrequently used and are included in the subfigure to demonstrate prescribing trends. The plot in the upper-left corner of the panel includes anticonvulsants and SNRIs, as these drug classes were infrequently prescribed and it was difficult to appreciate prescribing changes in comparison with more frequently prescribed drug classes. Dashed lines represent a linear regression on unique patient/prescription counts. (D) First-time prescriptions for SSRIs for unique individual patients from 2011 through 2020 demonstrated an increase in the use of sertraline and escitalopram but a decrease in the use of citalopram, with a mean year-over-year change of 14.2%, 18.2%, and −9.8%, respectively. Fluvoxamine, paroxetine, and vortioxetine were rarely used and are included in the subfigure to demonstrate prescribing trends. The plot in the upper-left corner of the panel includes fluvoxamine, paroxetine, and vortioxetine, as these drugs were infrequently prescribed and it was difficult to appreciate prescribing changes in comparison with more frequently prescribed drugs. Dashed lines represent a linear regression on unique patient/prescription counts. (E) Total SSRI use and share of total first-time prescriptions for SSRIs by individual drug for unique individual patients from 2011 through 2020.



ADHD, attention-deficit/hyperactivity disorder; PGx psych, psychiatric drugs classified as CPIC level A/B; *SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor (including vortioxetine); TCA, tricyclic antidepressant.*

the evidence is rated as weaker than for CPIC level A medications, CPIC level B gene-drug pairs are often included in clinical implementation.[9]

There are several key limitations to this study. First, this study did not include analysis of medication dosing, duration of use, indication, or existing PGx results.[10–12]

Secondly, as a single center, retrospective, cross-sectional study, these results are subject to biases that could affect both the internal and external validity of our findings. Our findings may not apply to institutions in other geographic areas or serving different patient populations. Internal changes at NCH, including provider changes, may have had an effect on our findings. Additionally, we used CPIC guidelines to define potential actionability in this study. While the CPIC guidelines may be used for both adults and pediatrics, the data supporting their use in pediatrics are less well established. Finally, we did not include psychiatric medications without PGx implications, which prevents an accurate estimation of opportunities for PGx testing, because testing may be considered prior to medication use or in scenarios where a CPIC-rated medication was not ultimately prescribed. This also underestimates the overall increase in psychiatric medication prescriptions.

Given the worsening mental health crisis and increasing evidence demonstrating benefits of PGx testing for mental health conditions, the data presented here suggest an opportunity to provide PGx-guided care. Further research is necessary to optimize implementation of PGx testing into the care of pediatric patients.

Article Information

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