Pharmacogenetic Testing and Therapeutic Drug Monitoring Of Sertraline at a Residential Treatment Center for Children and Adolescents: A Pilot Study

Kate France[1]; David Ammend, MD[2]; Jacob Brown, PharmD, MS[1]

[1]University of Minnesota College of Pharmacy, Duluth, Minnesota; [2]Northwest Passage, Frederic, Wisconsin

Abstract

***Background**: Sertraline is commonly prescribed to children for the treatment of anxiety and major depressive disorder and is metabolized in part by CYP2C19. While dosing recommendations based on CYP2C19 genotype exist, there is sparse data in children on the relationship between sertraline concentrations and CYP2C19 genotype. Additionally, although rarely utilized in the United States, therapeutic drug monitoring can also help to guide dosing. The primary objective of this pilot study was to compare sertraline concentrations with CYP2C19 genotype. Secondary objectives included exploring the feasibility of using pharmacogenetic testing and therapeutic drug monitoring in a residential treatment center for children and adolescents. **Methods**: This study was a prospective, open-label study of children prescribed sertraline being treated at a residential treatment center for children and adolescents. Individuals were included if they were < 18 years of age, taking sertraline for at least 2 weeks allowing them to reach steady-state concentrations, being treated through the residential treatment program, and able to understand and speak English. **Results**: A total of 20 participants (80% female) completed all study procedures, including pharmacogenetic testing and therapeutic drug monitoring, with an average age of 15.4 years (range: 9-17 years). Forty percent (n=8) of participants had a diagnosis of Generalized Anxiety Disorder, while 30% (n=6) had a diagnosis of Major Depressive Disorder. Overall, average sertraline and desmethylsertraline concentrations were 21.1 ng/ml (range: 1-78 ng/ml) and 52.4 ng/ml (range: 1-258 n/ml). Based on CYP2C19 genotypes, 60% (n=12) were normal metabolizers, 10% (n=2) were intermediate metabolizers, and 30% (n=6) were rapid metabolizers. Daily sertraline dose (mg/day) accounted for a significant amount of the observed variability in sertraline ($p<0.0001$; $r^2=0.62$) and desmethylsertraline concentrations ($p<0.001$; $r^2=0.45$). When comparing weight-based dosing by sertraline and desmethylsertraline concentrations, sertraline daily dose by weight (mg/kg/day) also accounted for a significant amount of the observed variability in sertraline ($p<0.0001$; $r^2=0.60$) and desmethylsertraline ($p<0.0001$; $r^2=0.59$) concentrations. Average daily and weight-based doses for CYP2C19 intermediate, normal, and rapid metabolizers were 75 mg/day, 87.5 mg/day, and 79.2 mg/day and 1.5 mg/kg/day, 1.3 mg/kg/day, and 1.1 mg/kg/day, though these were not significantly different. **Conclusion**: This small, pilot study showed sertraline dose to be significantly associated with sertraline and desmethylsertraline concentrations. No differences were noted between CYP2C19 metabolizer groups, likely due to the limited sample size. These results also suggest that ordering pharmacogenetic testing and therapeutic drug monitoring in the setting of a child and adolescent residential treatment center is feasible.*

Keywords: pharmacogenomics, pharmacokinetics, sertraline, pediatrics, genotype, CYP2C19, SSRIs

Introduction

Depression and anxiety are becoming increasingly common in children and adolescents, and treating these conditions will be vitally important going forward. Sertraline is commonly prescribed for children in the treatment of generalized anxiety disorder and major depressive disorder.[1] Children and adolescents are often started at 25 mg daily and then titrated based on response to a maximum dose of 200 mg.[2] In comparison to adult populations, children have lower sertraline concentrations, yet experience more side effects.[3] Sertraline is primarily metabolized by cytochrome p450 2C19 (CYP2C19) into its less active metabolite, desmethylsertraline. There are multiple enzymes involved within this metabolic pathway, including CYP3A4, CYP2C9, and CYP286, but the impact of CYP2C19 has shown to be the most significant.[9] To better understand the clinical implementation, precision medicine tools such as pharmacogenomics (PGx) and therapeutic drug monitoring (TDM) may be used to better improve clinical outcomes with sertraline.

PGx utilizes genetic information to better understand an individual's response to a medication, and the Clinical Pharmacogenetics Implementation Consortium (CPIC) provides dosing guidelines for a number of drug/gene pairs, including sertraline/CYP2C19.[4] Clinical PGx testing is completed in one of two ways: proactively, i.e., before the medication is started, or reactively, i.e., when a patient has a therapeutic failure or adverse effect. Depending on the gene, patients are typically grouped into one of five metabolizer phenotypes: poor, intermediate, normal (formerly extensive), rapid, or ultrarapid.[5] CYP2C19 has known variants resulting in loss of function alleles (e.g., *2, *3) or increased function alleles (e.g., *17).[6] Adults with decreased CYP2C19 activity (i.e., those with *2 and/or *3 alleles) may have higher than expected sertraline concentrations, while those with increased CYP2C19 activity (i.e., those with one or two *17 alleles) have recently been shown to not have significantly different concentrations as

Corresponding author: Jacob T. Brown, PharmD, MS
Assistant Professor
University of Minnesota, College of Pharmacy
1110 Kirby Drive, 232 Life Sciences
Duluth, MN, 55812
Phone: 218-726-6028; Email: jtbrown@d.umn.edu

DOI: https://doi.org/10.24926/iip.v13i4.5035

compared to normal metabolizers.[7] These differences in concentration are well described in adults; however, data in pediatric populations are less robust.[8,9]

TDM is the clinical measurement of drug concentrations at predefined intervals to maintain a consistent concentration of a specific drug in the patient's bloodstream, which can be used to optimize a patient's medication regimen.[10] In a naturalistic study of children and adolescents 8-16 years of age describing serum sertraline levels, concentrations ranged from 4-121 ng/mL.[3] In several other psychiatric medications, the concentration ranges in children are considerably different as compared to adults, suggesting the therapeutic range in children may differ from that of adults.[11,12] The defined sertraline trough concentrations reference range of 10-150 ng/mL from a comprehensive review by Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) in 2005 was based on a reference range for adults and not adolescent participants; however, in its 2017 update, the AGNP team found concentrations to be similar when comparing adults to adolescents.[13] This range comes from a study done by Lundmark et al, wherein the effective sertraline concentration range was determined to be 10-150 ng/mL.[14] Additional factors have been considered when determining this range, such as the binding of sertraline to the serotonin transporters (SERT). Bråten et al accepted the lower boundary of the AGNP Consensus Guidelines for Therapeutic Drug Monitoring, yet found that approximately 80% of SERTs were bound with a serum trough concentration of 75 ng/mL, suggesting a more reasonable reference range to be 10-75 ng/mL.[7] Although not absolute, reference ranges can be useful in determining whether patients are receiving too much or too little of a medication as further discussed in the AGNP guidelines.[13]

PGx and TDM are complementary tools for medication management and are especially relevant in pediatric populations, which often require additional considerations.[15-17] These include biochemical and physiological changes that occur in the developing child causing marked differences in both pharmacokinetic and pharmacodynamic parameters compared to adults. According to Gerlach et al, pediatric psychiatric medication dosing requires special considerations due these differences.[11] This lack of data in pediatric populations frequently results in off-label usage, raising questions concerning safety and efficacy.[18] Taurines et al reported that the number of side effects reported in children and adolescents was found to occur at a higher frequency in those with psychiatric comedications, demonstrating the need for a better understanding of psychotropic medication utilization in pediatric populations.[3]

While PGx studies of sertraline in children and adolescents are limited, overall sertraline concentrations are described in this population. The concentrations of sertraline and desmethylsertraline and their relative ratio may provide important information about metabolic processes in the body. By classifying the different genotype groups by their predicted phenotype, it is possible to compare the differences between poor, intermediate, normal, rapid, and ultrarapid metabolizers.[6,19-20] From this, novel information regarding pediatric metabolism of sertraline based on the stratification of their *CYP2C19* genotype may be described, adding to the limited existing literature. The primary objective of this pilot study was to compare steady-state sertraline and desmethylsertraline trough concentrations in children with dose and *CYP2C19* genotypes. Secondary objectives included exploring the feasibility of using PGx and TDM in children and adolescents at a residential treatment center.

Methods

This study was a prospective, open-label study of children prescribed sertraline being treated at a residential treatment center for children and adolescents. Individuals were included if they were <18 years of age, taking sertraline for at least 2 weeks allowing them to reach steady-state concentrations, being treated through the residential treatment program, and able to understand and speak English. Participants were excluded if they were ≥ 18 years of age or not taking sertraline. This study was approved by the University of Minnesota Institutional Review Board (#00000612).

Study Procedures

Each parent or guardian provided written permission while each participant provided written assent. Following permission/assent, each participant provided a buccal sample for PGx testing through a Clinical Laboratory Improvement Amendments-certified laboratory. Participants also submitted a 2-mL blood sample through a local regional medical center to measure steady-state trough concentrations of sertraline and its CYP2C19 metabolite desmethylsertraline through MedTox© (St. Paul, MN). Blood samples were drawn as close to the next dose as feasible, and were combined with existing blood draws when possible. For sertraline and desmethylsertraline concentrations below the lower level of quantification, these values were assigned a value of 1 ng/mL.

Individuals with the *1/*1 genotype were categorized as normal metabolizers, those with a *1/*17 genotype were categorized as rapid metabolizers, and those who were *1/*2 were categorized as intermediate metabolizers. No individuals tested had the *3 allele.

Data analysis

Average serum concentrations of sertraline and desmethylsertraline were compared utilizing ANOVA tests across increased, normal, and decreased CYP2C19 metabolizer groups. Where ANOVA tests were significant, Tukey's HSD tests were used to compare between the CYP2C19 metabolizer groups. Ratios of sertraline:desmethylsertraline were analyzed in a similar fashion.

Results

Twenty participants (80% female) with an average age of 15.4 years (range: 9-17 years) completed all study procedures. Sixty-five percent (n=13) of participants were White, 15% (n=3) Black/African American, 10% (n=2) Asian, 5% (n=1) American Indian/Alaska Native, and 5% (n=1) Other. No individuals identified as Hispanic. Forty percent (n=8) of participants had a diagnosis of Generalized Anxiety Disorder (ICD F-41.1), while 30% (n=6) had a diagnosis of Major Depressive Disorder (ICD F-33.9). The mean sertraline dose was 83.75 mg/day with a range of 25-200 mg/day, and an average weight-based dose of 1.3 mg/kg/day (stdev: 0.75). Overall, average sertraline and desmethylsertraline concentrations were 21.1 ng/ml (range: 1-78 mcg/ml) and 52.4 mcg/ml (range: 1-258 mcg/ml). Based on *CYP2C19* genotypes, 60% (n=12) were normal metabolizers, 10% (n=2) were intermediate metabolizers, and 30% (n=6) were rapid metabolizers. Complete demographic data can be found in **Table 1**.

Absolute sertraline daily dose (mg/day) accounted for a significant amount of the observed variability in sertraline ($p<0.0001$; $r^2=0.62$) and desmethylsertraline concentrations ($p<0.001$; $r^2=0.45$). When compared weight-based dosing by sertraline and desmethylsertraline concentrations, sertraline daily dose by weight (mg/kg/day) also accounted for a significant amount of the observed variability in sertraline ($p<0.0001$; $r^2=0.60$) (**Figure 1A**) and desmethylsertraline ($p<0.0001$; $r^2=0.59$) (**Figure 1B**) concentrations.

Average daily and weight-based doses for CYP2C19 intermediate, normal, and rapid metabolizers were 75 mg/day, 87.5 mg/day, and 79.2 mg/day and 1.5 mg/kg/day, 1.3 mg/kg/day, and 1.1 mg/kg/day, though neither of these were significantly different ($p>0.05$). Between CYP2C19 intermediate, normal, and rapid metabolizers, average sertraline trough concentrations were 38 ng/mL, 17.3 ng/mL, and 23 ng/mL (**Figure 2A**), while desmethylsertraline concentrations were 79 ng/mL, 49.4 ng/mL, and 49.5 ng/mL (**Figure 2B**), also not significant ($p>0.05$). Sertraline / desmethylsertraline concentrations across CYP2C19 intermediate, normal, and rapid phenotypes were 0.46, 0.38, and 0.41 (**Figure 2C**). When excluding the largest outlier in the normal CYP2C19 metabolizer group, significant differences between CYP2C19 metabolizer groups and average sertraline concentrations were noted ($p=0.05$); however, these were not significant when directly comparing the groups with the largest differences, intermediate and normal metabolizers (38 ng/mL vs 11.8 ng/mL; $p=0.1$). Significant differences were also noted between CYP2C19 metabolizer groups and average desmethylsertraline concentrations ($p=0.02$); with significantly higher concentrations observed in intermediate metabolizers (79 ng/mL) as compared to normal metabolizers (30.5 ng/mL; $p=0.02$).

Discussion

The completion of the Human Genome Project marked a major accomplishment in the field of genomics and opened the door to new advancements in precision medicine. In conjunction with the International HapMap Project, the Human Genome Project made available a large amount of gene-response associations. Due to the high-priority nature of advancing PGx into clinical practice, several critical developments in collaborative research networks have spurred the creation of several key PGX databases to better support implementation efforts.[4,21] These databases provide key information for prescribing physicians and pharmacists utilizing PGx data. However, most data is for adult populations. Children and adolescents are a unique patient population where PGx testing may be of value in the long term. Children's hospitals implementing PGx testing typically have to adopt PGx guidelines developed primarily based on this adult data.[15] Thus, it is imperative that not only the process of utilizing PGx in children is optimized, but also that additional research in children is conducted to help better inform dosing recommendations based on PGx results.

Sertraline, often prescribed for the treatment of depression and anxiety in children and adolescents, has limited research relative to the impact of *CYP2C19* genotype variation on serum concentrations in children. While this study confirmed that dose plays a significant role in explaining the variability related to exposure of both sertraline and desmethylsertraline, it was not powered to identify differences across different *CYP2C19* genotypes. Though not currently standard of care for sertraline, both PGx testing and TDM may be useful tools for clinicians when starting children on sertraline and/or titrating their dose. The CPIC CYP2C19/sertraline guideline currently recommends a 50% dose reduction in poor metabolizers or selecting a medication not metabolized by CYP2C19, while TDM can be utilized to potentially explain a lack of therapeutic response or adverse effects.[20]

Pharmacokinetic modeling created by Strawn *et al* showed that children who have reduced CYP2C19 activity experienced greater exposure to sertraline, which may support the argument for using CYP2C19 genotyping to help guide dosing.[12] Similarly, work by Rudberg *et al* showed that the presence of loss of function CYP2C19 alleles (i.e., *2 or *3), or what constitutes the poor and intermediate metabolizer groups, revealed significant influence on serum concentrations in both sertraline and desmethylsertraline in adult psychiatric patients.[19] Additionally, Bråten *et al* found that poor metabolizers experienced an average concentration increase of more than double when compared to normal metabolizers, informing their recommendation that poor and intermediate metabolizers should receive a 60% and 25% decrease in dose, respectively.[7] Rudberg *et al* additionally found that those with defective alleles in their *CYP2C19* genotype (what would constitute poor and intermediate metabolizers) experienced serum concentrations of sertraline more than three times

higher than those with the wildtype expression.[19] Lastly, research by Wang *et al* also indicates that poor metabolizers show an increased risk of side effects when placed on similar doses as the normal metabolizer counterparts, possibly due to increased exposure resulting in toxicity.[5] With these studies in mind, knowledge of *CYP2C19* genotype prior to dosing may help clinicians to reduce the variability currently observed.

TDM can be useful in several ways, including providing clinicians an idea of adherence to a specific dosing regimen, whether someone is above or below the therapeutic range (and thus over or underdosed), and potentially improving therapeutic outcomes. A study done by Reis *et al* explored the significance of TDM and its implications for patient adherence to drug dosing regimens. The variations of concentrations of sertraline versus desmethylsertraline showed strong indications of hidden and partial non-adherence,[22] which may be significant as it can be used to monitor medication adherence to gain a better overall understanding of the patient's metabolism and possible drug-drug interactions.

CPIC works to address the barriers to implementation in PGx by producing open access, peer-reviewed, and evidence-based gene/drug clinical practice guidelines. These guidelines commonly support implementation by providing valuable knowledge to the clinician ordering PGx testing.[4,23] This knowledge is critical because, as found in research by Avello *et al*., over 90% of respondents stated they would have more confidence in ordering and interpreting PGx testing with the assistance of some form of PGx expert.[18] Furthermore, recent surveys found that pediatricians feel as though they are lacking in the knowledge and education needed to provide PGx in their practice, as even medications with known PGx variability are prescribed without genotyping.[16, 18]

There are three primary challenges currently creating barriers to widespread PGx implementation, including cost, uniformity, and knowledge. Although cost was not an issue in the context of this study, it is something the authors acknowledge as a barrier to implementation. As for uniformity, Ramsey *et al* discuss the variations in the way PGx is utilized to varying degrees of success.[17] Some order the tests for drug selection, others for titration and dose determination, and some others utilize it for a combination therein. Some receive help from pharmacists institutionally, and in the community pharmacy setting pharmacists are a common touchpoint for general PGx questions.[24] While implementing PGx in any capacity can be viewed as a step in the right direction, questions are being raised about the efficacy of these different practices and the quality of care provided in each. Arguably the most significant barrier to implementation comes in the lack of knowledge providers have regarding PGx. There is a growing need to develop an evidence-based implementation methodology for specific PGx testing in children and adolescents. Challenges include a lack of understanding of the ontogeny of drug-metabolizing enzymes and transporters in different phases of human development, lack of integration into clinical trials, lack of definitive guidelines for this patient population, understanding of the economic value of testing, and deciphering the multivariate nature of most drug effects with the contribution of physiological and pathological factors.[18, 25]

One final consideration of significance for the study is based on a point brought up by Brown, *et al.*, as much of this implementation research occurs within large-scale children's specialty institutions; this study sought trends found in a small, rural inpatient facility. Regardless of the size or scale of the facility, one thing is for certain: to have the best chance at proper utilization of PGx in pediatric populations, there needs to be an increase in the education across all professional levels to provide the most effective and accurate knowledge on the subject to our patients.[24]

Although there was limited significance found in this study, the results generally followed expected trends and provide a framework for future research, as well as a process for clinically ordering PGx testing at a residential treatment center for children and adolescents. This may be achieved on a larger scale project, as one shortcoming of this study was the limited size of the cohort. The sample size was highly specific in that patient influx was slow and enrollment within the study was sometimes difficult to achieve. The global COVID-19 pandemic caused the study to end prematurely with an overall sample size of 20, only two of which were intermediate metabolizers for CYP2C19, limiting data from this metabolizer group. Generally speaking, the spread of stratification was expected, as it mirrors that described in this population.[3] However, there was a scarcity of genotypes at the ends of the CYP2C19 activity spectrum, with no ultra rapid or poor metabolizers as a part of this study. A larger sample size from a similar population would also provide more data for this research and provide a better understanding of the implications of the findings for the field.

In summation, this pilot study was done to explore the relationship between sertraline drug concentrations stratified by CYP2C19 genotype, with an emphasis on the implementation of therapeutic drug monitoring in combination with PGx testing within a residential pediatric population. While not powered enough to extrapolate many findings, any additional information that can be provided to this field helps to fill critical gaps in existing knowledge. Future studies in this area could include clinical efficacy data utilizing a validated tool for PGx and TDM.

The opinions expressed in this paper are those of the authors.

Conflict of Interest: We have no conflicts of interest to disclose at this time.

References

1. Strawn, J. R., Geracioti, L., Rajdev, N., Clemenza, K., & Levine, A. (2018). Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. Expert opinion on pharmacotherapy, 19(10), 1057–1070. https://doi-org.ezp3.lib.umn.edu/10.1080/14656566.2018.1491966
2. Poweleit EA, Aldrich SL, Martin LJ, Hahn D, Strawn JR, Ramsey LB. Pharmacogenetics of Sertraline Tolerability and Response in Pediatric Anxiety and Depressive Disorders. J Child Adolesc Psychopharmacol. 2019 Jun;29(5):348-361. doi: 10.1089/cap.2019.0017. Epub 2019 May 8. PMID: 31066578.
3. Taurines R, Burger R, Wewetzer Ch, Pfuhlmann B, Mehler-Wex C, Gerlach M, Egberts K. The relation between dosage, serum concentrations and clinical outcome in children and adolescents treated with sertraline: a naturalistic study. Ther Drug Monitoring 2013. 35(1):84-91
4. Relling, M. V., Klein, T. E., Gammal, R. S., Whirl-Carrillo, M., Hoffman, J. M., & Caudle, K. E. (2020). The Clinical Pharmacogenetics Implementation Consortium: 10 Years Later. Clinical pharmacology and therapeutics, 107(1), 171–175. https://doi-org.ezp3.lib.umn.edu/10.1002/cpt.1651
5. Wang JH, Liu ZQ, Wang W, Chen XP, Shu Y, He N, Zhou HH. Pharmacokinetics of sertraline in relation to genetic polymorphism of CYP2C19. Clin Pharmacol Ther. 2001 Jul;70(1):42-7. doi: 10.1067/mcp.2001.116513. PMID: 11452243.
6. Yuce-Artun N, Baskak B, Ozel-Kizil ET, Ozdemir H, Uckun Z, Devrimci-Ozguven H, Suzen HS. Influence of CYP2B6 and CYP2C19 polymorphisms on sertraline metabolism in major depression patients. Int J Clin Pharm. 2016 Apr;38(2):388-94. doi: 10.1007/s11096-016-0259-8. Epub 2016 Jan 30. PMID: 26830411.
7. Bråten LS, Haslemo T, Jukic MM, Ingelman-Sundberg M, Molden E, Kringen MK. Impact of CYP2C19 genotype on sertraline exposure in 1200 Scandinavian patients. Neuropsychopharmacology. 2020 Feb;45(3):570-576. doi: 10.1038/s41386-019-0554-x. Epub 2019 Oct 24. PMID: 31649299; PMCID: PMC6969041.
8. Walkup JT, Albano AM, Piacentini J, et al: Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med 2008; 359(26):2753-2
9. Huddart, Rachela; Hicks, J. Kevin; Ramsey, Laura B.c; Strawn, Jeffrey R.d; Smith, D. Maxe, PharmGKB summary: sertraline pathway, pharmacokinetics, Pharmacogenetics and Genomics: February 2020 - Volume 30 - Issue 2 - p 26-33. doi: 10.1097/FPC.0000000000000392
10. Kang, J. S., & Lee, M. H. (2009). Overview of therapeutic drug monitoring. The Korean journal of internal medicine, 24(1), 1.
11. Gerlach M, Egberts K, Dang SY, Taurines R, Mehler-Wex C, Romanos M. Therapeutic drug monitoring as a measure of proactive pharmacovigilance in child and adolescent psychiatry. Expert Opinion on Drug Safety 2016. 15(11)1:1477-82.
12. Strawn, J. R., Poweleit, E. A., & Ramsey, L. B. (2019). CYP2C19-guided escitalopram and sertraline dosing in pediatric patients: a pharmacokinetic modeling study. Journal of child and adolescent psychopharmacology, 29(5), 340-347.
13. Hiemke, C., Bergemann, N., Clement, H. W., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., Mössner, R., … Baumann, P. (2018). Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry, 51(1-02), 9–62. https://doi-org.ezp3.lib.umn.edu/10.1055/s-0043-116492
14. Lundmark, J., Bengtsson, F., Nordin, C., Reis, M., & Wålinder, J. (2000). Therapeutic drug monitoring of selective serotonin reuptake inhibitors influences clinical dosing strategies and reduces drug costs in depressed elderly patients. Acta Psychiatrica Scandinavica, 101(5), 354-359.
15. Gregornik, D., Salyakina, D., Brown, M., Roiko, S., & Ramos, K. (2021). Pediatric pharmacogenomics: challenges and opportunities: on behalf of the Sanford Children's Genomic Medicine Consortium. The Pharmacogenomics Journal, 21(1), 8-19.
16. de Beaumais, T. A., & Jacqz-Aigrain, E. (2018). Pharmacogenetics: applications to pediatric patients. Advances in Pharmacology, 83, 191-215.
17. Ramsey, L. B., Bishop, J. R., & Strawn, J. R. (2019). Pharmacogenetics of treating pediatric anxiety and depression. Pharmacogenomics, 20(12), 867-870.
18. Avello, K., Bell, M., Stein, Q., Bares, V., Landsverk, M., Salyakina, D., ... & Hoyme, H. E. (2021). Perspectives of Pediatric Providers Regarding Clinical Use of Pharmacogenetics. South Dakota Medicine, 74(7).
19. Rudberg I, Hermann M, Refsum H, Molden E. Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. Eur J Clin Pharmacol. 2008 Dec;64(12):1181-8. doi: 10.1007/s00228-008-0533-3. Epub 2008 Aug 3. PMID: 18677622.
20. Hicks JK et al. Clinical PGx Implementation Consortium Guidelines for CYP2D6 and CYP2D19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clin Pharmacol Ther 2015. 98(2);127-34
21. Barbarino, J. M., Whirl-Carrillo, M., Altman, R. B., & Klein, T. E. (2018). PharmGKB: A worldwide resource for pharmacogenomic information. Wiley interdisciplinary reviews. Systems biology and medicine, 10(4), e1417. https://doi-org.ezp3.lib.umn.edu/10.1002/wsbm.1417
22. Reis M, Akerblad AC, Ekselius L et al. Partial compliance as determined from plasma levels of sertraline and its metabolite in depressed patients in primary care. J Clin Psychopharmacol 2010; 30 : 746 – 748
23. Brown, J. T., Bishop, J. R., Sangkuhl, K., Nurmi, E. L., Mueller, D. J., Dinh, J. C., ... & Leeder, J. S. (2019). Clinical pharmacogenetics implementation consortium guideline for cytochrome P450 (CYP) 2D6 genotype and atomoxetine therapy. Clinical Pharmacology & Therapeutics, 106(1), 94-102.
24. Brown, J. T., Ramsey, L. B., Van Driest, S. L., Aka, I., & Colace, S. I. (2021). Characterizing pharmacogenetic testing among children's hospitals. Clinical and translational science, 14(2), 692-701.
25. Petry N, Lupu R, Gohar A, Larson EA, Peterson C, Williams V, Zhao J, Wilke RA, Hines LJ. CYP2C19 genotype, physician prescribing pattern, and risk for long QT on serotonin selective reuptake inhibitors. Pharmacogenomics. 2019 Apr;20(5):343-351. doi: 10.2217/pgs-2018-0156. Epub 2019 Apr 15. PMID: 30983508; PMCID: PMC6562837.

Table 1.

Subject ID	Age	Weight	BMI	CYP2C19 Phenotype	CYP2C19 Genotype	Sex	Race	Dose (mg)	Dose (mg/kg)	Sertraline Concentration	Desmethylsertraline Concentration	Sertraline: Desmethylsertraline Ratio
SER01	16	78	29.6	*1/*1	Normal	F	W	200	2.56	46	60	0.77
SER02	16	121	42.8	*1/*1	Normal	F	W	50	0.41	<10	<10	-
SER04	9	33	17.5	*1/*1	Normal	M	W	25	0.76	<10	44	-
SER05	15	74	27.2	*1/*2	Intermediate	F	W	50	0.68	20	52	0.38
SER07	16	57	22.7	*1/*1	Normal	F	W	75	1.32	<10	16	-
SER08	15	63	25.6	*1/*1	Normal	F	O	50	0.79	11	25	0.44
SER11	14	55	19.3	*1/*17	Rapid	M	W	75	1.36	11	33	0.33
SER12	17	70	26.7	*1/*1	Normal	F	W	50	0.71	<10	19	-
SER13	17	59	21.2	*1/*1	Normal	F	W	200	3.39	78	258	0.30
SER14	12	36	17.4	*1/*1	Normal	M	W	25	0.69	<10	28	-
SER15	17	67	24.3	*1/*1	Normal	F	A	50	0.75	13	36	0.36
SER16	17	74	28.6	*1/*17	Rapid	F	AA	100	1.35	25	55	0.45
SER17	17	60	24.7	*1/*1	Normal	F	W	100	1.67	11	24	0.46
SER18	15	115	35.0	*1/*17	Rapid	M	W	100	0.87	45	89	0.51
SER19	16	43	17.6	*1/*2	Intermediate	F	A	100	2.33	56	106	0.53
SER20	15	71	25.1	*1/*17	Rapid	F	AA	100	1.41	26	55	0.47
SER21	14	74	26.5	*1/*1	Normal	F	AI/AN	100	0.95	12	36	0.33
SER22	16	105	36.3	*1/*1	Normal	F	W	100	0.95	32	46	0.70
SER23	17	60	28.8	*1/*17	Rapid	F	W	50	0.83	30	47	0.64
SER24	16	87	29.7	*1/*17	Rapid	F	AA	50	0.57	<10	18	-

Legend. Sex: (M=Male) and (F=Female); Race: (A = Asian), (AA = African American), (American Indian/Alaska Native), (O = Other) (W = White)

Figure 1.

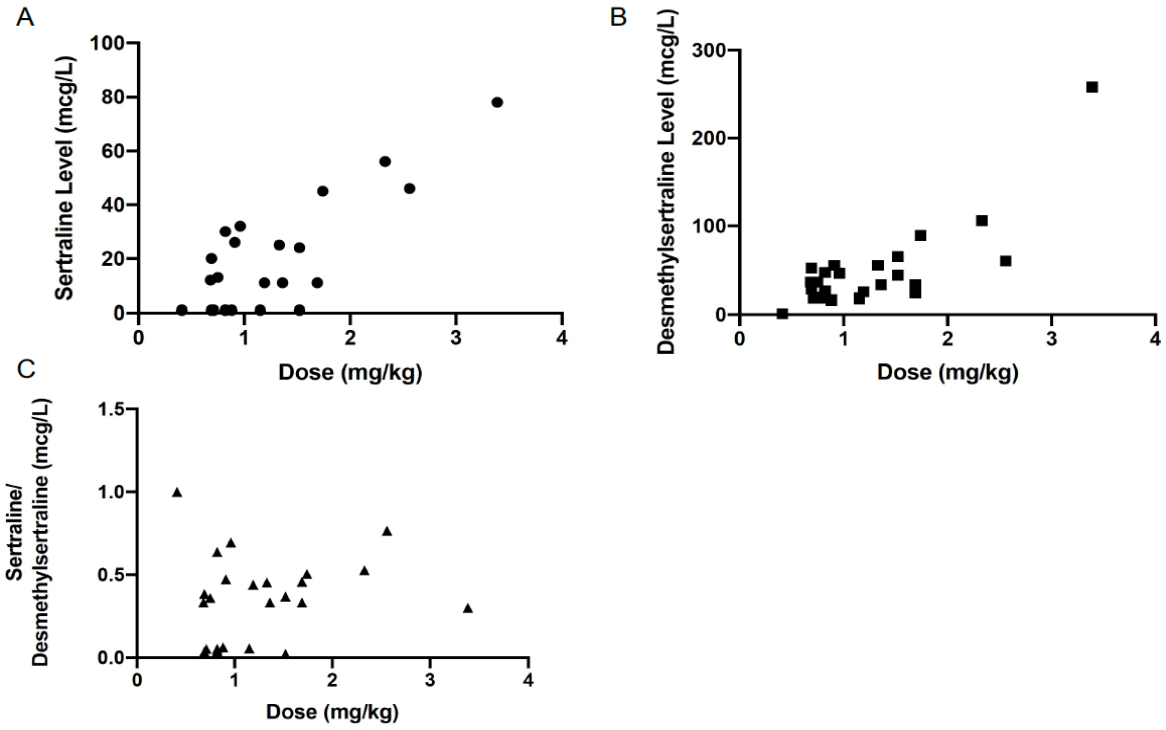

Figure 2.