JPPT | Single Center Prospective Study

Medication Management Through Collaborative Practice for Children With Medical Complexity: A Prospective Case Series

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OBJECTIVE Care coordination for children and youth with special health care needs and medical complexity (CYSHCN-CMC), especially medication management, is difficult for providers, parents/caregivers, and patients. This report describes the creation of a clinical pharmacotherapy practice in a pediatric long-term care facility (pLTCF), application of standard operating procedures to guide comprehensive medication management (CMM), and establishment of a collaborative practice agreement (CPA) to guide drug therapy.

METHODS In a prospective case series, 102 patients characterized as CYSHCN-CMC were included in this pLTCF quality improvement project during a 9-month period.

RESULTS Pharmacists identified, prevented, or resolved 1355 drug therapy problems (DTP) with an average of 13 interventions per patient. The patients averaged 9.5 complex chronic medical conditions with a median length of stay of 2815 days (7.7 years). The most common medications discontinued due to pharmacist assessment and recommendation included diphenhydramine, albuterol, sodium phosphate enema, ipratropium, and metoclopramide. The average number of medications per patient was reduced from 23 to 20. A pharmacoeconomic analysis of 244 of the interventions revealed a monthly direct cost savings of $44,304 ($434 per patient per month) and monthly cost avoidance of $48,835 ($479 per patient per month). Twenty-eight ED visits/admissions and 61 clinic and urgent care visits were avoided. Hospital readmissions were reduced by 44%. Pharmacist recommendations had a 98% acceptance rate.

CONCLUSIONS Use of a CPA to conduct CMM in CYSHCN-CMC decreased medication burden, resolved, and prevented adverse events, reduced health care-related costs, reduced hospital readmissions and was well-accepted and implemented collaboratively with pLTCF providers.

ABBREVIATIONS ADR, adverse drug reaction; AlOH-MgOH, aluminum hydroxide-magnesium hydroxide; CMC, children with medical complexity; CMM, comprehensive medication management; CPA, collaborative practice agreement; CPT, current procedural terminology; CTCAE, Common Terminology Criteria for Adverse Events; CYSHCN-CMC, children and youth with special health care needs and medical complexity; DTP, drug therapy problems; ED, emergency department; MRCI, Medication Regimen Complexity Index; NaK-phosphate, sodium and potassium phosphate; NaPhos-enema, sodium phosphate enema; PHIS, Pediatric Health Information System; pLTCF, pediatric long-term care facility

KEYWORDS adverse drug reactions; children with disability; chronic disease; drug-related side effects; economics; long-term care; medication management; pharmaceutical; pharmacist

J Pediatr Pharmacol Ther 2024;29(2):119–129

DOI: 10.5863/1551-6776-29.2.119

Introduction

Children and youth with special health care needs and medical complexity (CYSHCN-CMC) have numerous significant chronic health conditions that affect multiple organ systems and result in functional limitations, high health care need or utilization and often require the use of medical technology.[1–4] An example of this would be a child who experienced decreased oxygenation to the brain during the birthing process, ultimately resulting in hypoxic-ischemic encephalopathy who now lives with epilepsy, respiratory failure requiring tracheostomy and mechanical ventilatory support, gastrostomy tube dependence, excessive secretions, cortical blindness and endocrinologic disorders. These patients face many unmet needs, especially the subpopulations affected by multimorbidity and polypharmacy.[5–12] These patients account for almost 30% of all pediatric health care costs while representing about 1% of the pediatric population.[1,13] Numerous strategies have been employed recently to improve care access

and reduce adverse events, including patient-centered medical homes,[14–16] telemedicine,[17] and multidisciplinary team-based care,[18] among others, but routine utilization of pediatric clinical pharmacy services for comprehensive medication management (CMM) has not been a major initiative.[19]

CMM in Children With Complex Chronic Conditions. Complex chronic conditions have been previously defined by as "any medical condition that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several different organ systems or one organ system severely enough to require specialty pediatric care and probably some period of hospitalization in a tertiary care center".[20]

CYSHCN-CMC often have many complex chronic conditions necessitating intricate care plans that include multiple medications, various subspecialty involvement and technology dependence which can make discharge to home difficult. CYSHCN-CMC may be transferred to pediatric long-term care facilities (pLTCF) where a new team of physicians, advanced practice providers, nurses and respiratory therapists are required to coordinate all discussions with subspecialists and assess medication management issues, especially during transitions of care. An evaluation of admission medication reconciliation in CYSHCN-CMC at an acute care hospital revealed high rates of incorrect medication orders in more than half of patients.[21] Provision of CMM or medication therapy management by pharmacists has been identified as a service that would likely benefit CYSHCN-CMC and significantly reduce medication regimen complexity.[22]

Drug Therapy Problems in CYSHCN-CMC (ADR Risk, Polypharmacy, and Off-Label Medication Use). CYSHCN-CMC are known to have frequent hospitalizations, to be on multiple medications and to be at higher risk of adverse drug reactions (ADRs).[23–25] ADR-related emergency department utilization is nearly 5 times more likely in pediatric patients with at least one complex chronic condition.[26] High rates of preventable ADRs identified by CMM on hospital admission have been reported in CYSHCN-CMC, particularly in those receiving at least 5 chronic medications.[21] Polypharmacy is a documented problem in this group, as many CYSHCN-CMC are frequently exposed to chronic daily polypharmacy (≥ 5 medications), with complex regimens that span multiple therapeutic classes and include high risk medications.[22,27–30] Polypharmacy increases the risk of drug-drug interactions and subsequent potential ADRs, especially in children with more than 3 complex chronic conditions.[30] The incidence of ADRs may also be affected by the high rate of off-label and unlicensed medication use in the pediatric population.[31–33]

Hospital Readmissions and Cost Savings/Cost Avoidance. Hospital readmission accounts for the largest share of subsequent costs after an index hospitalization, and payers are targeting this metric to reduce unnecessary health care spending.[1,34,35] Thirty-day hospital readmission rates in children with complex chronic conditions vary from 13% to 40% based on the degree of medical complexity and technology dependence.[34–36] The number of discharge medications and complex chronic conditions in CYSHCN-CMC have been associated with hospital readmissions.[34]

Avoidable expenditure in CYSHCN-CMC in the ambulatory setting is not isolated to hospital readmissions. Direct cost savings, or "hard costs," are achievable with interventions such as discontinuation of an unnecessary medication or laboratory test. Cost avoidance, or "soft costs," refers to potential money saved if a potential ADR had not been mitigated or prevented. The financial impact of pharmacist interventions for cost avoidance in pediatric ambulatory care clinics has been characterized, but not in the pLTCF setting.[37]

The purpose of this case series is to describe a pediatric pharmacotherapy practice focused on provision of CMM through establishment of a collaborative practice agreement (CPA) for patients admitted to a pLTCF with complex medical conditions (CYSHCN-CMC), describe this vulnerable patient population, report on pharmacotherapeutic interventions, quantify the cost savings and cost avoidance associated with pharmacist intervention and describe the impact of pharmacist involvement at a pLTCF on hospital readmission.

Methods and Materials

Pediatric Clinical Pharmacist Team Description. Perfecting Peds, LLC is a pediatric pharmacist owned and operated consultative pharmacy group, consisting of 7 highly skilled pediatric pharmacists with over 70 years of combined extensive experience in medication therapy management, drug information and patient/caregiver counseling. The Doctor of Pharmacy staff at Perfecting Peds are either Board Certified Pediatric Pharmacotherapy Specialists or have completed some or all of residency training in the pediatric setting. Many are nationally/internationally recognized for their contributions to pediatric pharmacy practice and heavily published in the pediatric literature.

Perfecting Peds is contracted in numerous pediatric care settings including pLTCF, medical daycares, acute care rehabilitation and ambulatory clinics, and cares for home-based private pay patients.

Targeted pLTCF Description. This suburban-based pLTCF receives patient referrals from major children's hospitals within a four-state radius. This pLTCF provides skilled nursing, rehabilitative care, respiratory care, and addresses issues such as growth, development, and education which can be complicated by the child's medical fragility. The prescriber team at this specific pLTCF includes one board-certified pediatric pulmonologist and two advanced practice providers

with extensive experience in caring for pLTCF patients. Additional members of the care team include nurses and respiratory therapists. Pharmacy services at this facility have been historically limited to a once-monthly pharmacist visit to evaluate expired medications, narcotic counts, medication passes, and compliance of state medication regulations.

Protocol Description. A prospective case series methodology was employed to study pediatric clinical pharmacist interventions for CYSHCN-CMC at a free-standing pLTCF.[38] Each pediatric clinical pharmacist entered into a CPA with the prescribers at the institution and obtained CPA state licensure. The CPA allowed for certain pre-approved interventions to occur without consultation of the prescribing provider, while other interventions required provider/pharmacist discussion (e.g., allowed for the clinical pharmacist to adjust the dosing weight on acetaminophen PRN orders without approval but required discussion/approval if adjusting a diazepam taper).

Patients were included in this study if they were admitted to the pLTCF during the study period (August 1, 2022–March 31, 2023) and if parental/guardian consent for participation in the CPA was obtained. Patients who did not meet the inclusion criteria were excluded.

Pediatric clinical pharmacists under the CPA were trained by JQ and HMB on the Perfecting Peds Comprehensive Medication Review protocol (available upon request from authors). These pharmacists then, per protocol, reviewed patient charts for progress notes (physician, nursing, consultant, respiratory therapy, nutrition, behavioral support, etc.), laboratory values, active orders (medication, laboratory, nutrition, nursing, physician), weight trends, chief medical conditions, past medical history, enteral feeding access, presence of tracheostomy, allergies, and medication administration records. These comprehensive chart reviews occurred at least once monthly per patient and as needed based on proactive provider outreach to the pediatric clinical pharmacist. A comprehensive consultant pharmacist progress note outlining assessments and recommended interventions was entered into the patient-specific chart each month which outlined pre-approved interventions as well as interventions that needed to be discussed with the pLTCF team and/or outside consultant subspecialties (e.g., Neurology, Endocrinology, etc.).

The consultant pharmacist progress note for each patient was reviewed monthly (JQ and HMB) to track the number of chronic medications, track number and type of interventions (including acceptance and rejection rate) and identify drug therapy problems (DTPs) using DocStation Electronic Health Record Software. Definitions/examples of DTPs are found in Table S1.

Certain interventions for DTPs required monitoring plan implementation after pharmacist intervention acceptance (e.g., recommendation to taper topiramate off required additional monitoring for seizure recurrence, obtaining basic metabolic panel to monitor sodium levels and acid/base status and determine if sodium citrate should be decreased or discontinued). The type of implemented monitoring plan was tracked at the time of monthly progress note review and further categorized.

Adverse drug reactions (ADRs) were tracked and categorized in 2 ways:

1. ADR monitored: the pharmacist identified that certain monitoring plans were missing to ensure the safety of medication administration and recommended that such a plan be implemented to prevent ADR (e.g., patients on antipsychotics without any metabolic panel monitoring ordered); or,
2. ADR managed: the pharmacist identified that a specific ADR was likely occurring secondary to a medication based on drug dosing references, primary literature, and clinical experience. The pharmacist then had discussions with the prescriber and nursing teams as well as consultant physicians to discuss the likelihood of causality. Each of the ADR managed events were deemed by the collective team to have been secondary to the medication and a plan was implemented to resolve or treat the ADR (e.g., on clonidine every 6 hours for autonomic storming and behavioral issues but experiencing hypotension/bradycardia necessitating holding of doses. Plan implemented to taper interval and monitor for blood pressure, heart rates and agitation/storming episodes to assess impact of intervention).

To further describe the complexity of pLTCF residents, each patient's active ICD-10 codes[39] were evaluated (HMB) to categorize and quantify those diagnoses defined as complex chronic conditions.[20]

Descriptive statistics are used for patient demographics and DTP frequency distributions.

Pharmacoeconomic Analyses. *Cost Avoidance (Soft Costs).* A pharmacoeconomic analysis was conducted using the methodology of Yung et al[37] to determine cost avoidance in the setting of ADR prevention. The standardized process map, developed by Yung et al,[37] was used for each ADR subtype to assure uniformity of ADR assessments. Drug information sources (Lexicomp, Micromedex, Natural Medicines Comprehensive Database, medication package inserts, and/or primary literature) were reviewed to identify common ADRs, drug interactions, and duplicate therapies among the medications. The specific references used for any individual intervention were at the discretion and expertise of the pediatric clinical pharmacist reviewing the patient chart. The World Health Organization Uppsala Monitoring Center causality categories were used to evaluate the probability that an ADR was related directly to the medication in question. The review team (JQ, HMB, EW) convened monthly to evaluate each DTP by using the Nesbit method to assign a probability coefficient of 0 (no

harm expected), 0.01 (very low), 0.1 (low), 0.4 (medium), or 0.6 (high) that each ADR would occur without pharmacist intervention.[40]

The review team (JQ, HMB, EW) then used the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to assign an expected care level to address the potential ADR. If a level of care could not be determined using the CTCAE method, consensus was based on clinical experience and discussion with the intervening pharmacist. Care levels were emergency department (ED) or hospital visit, ambulatory care clinic visit, and self-care. ED visits and hospitalizations were combined as one care level as some ED visits could lead to hospitalizations.

Charges for care were based on the Pediatric Health Information System (PHIS). PHIS data are gathered from the largest and most advanced US children's hospitals with the highest standards of pediatric care. Data from 51 pediatric hospitals within PHIS were used to determine that the average 2019 charge data for an ED visit or hospitalization was $48,692.[41]

Charge for ambulatory care visits was estimated by averaging charge data from 29 PHIS hospitals. Current procedural terminology (CPT) codes 99213, level 3, or intermediate office visit charges were used with an average of $205. Visits coded at this level are 15 minutes in duration with 1 problem evaluated.[42]

The average charge for self-care was set at $0. Many interventions related to ADRs could likely be managed by the facility or with over-the-counter medications and would not require an additional clinic visit.

Cost avoidance from reduced morbidity was calculated by multiplying the probability coefficient by the average charge of the care level assigned by the review team. For example, if an intervention was assigned a medium (0.4) probability of occurring and resulted in an ambulatory care clinic visit, the cost avoidance would be calculated as follows:

Probability coefficient (0.4) x care level ($205) = $82 total cost avoidance

Excluded interventions for the cost avoidance analysis included interventions related to treatment recommendations that did not prevent or manage adverse drug events (ADEs) (e.g., increasing an ibuprofen dose based on updated patient weight). Potential drug interactions were excluded if there were no medication changes or laboratory test orders necessary at the time of intervention documentation.

Cost Savings (Hard Costs). For scheduled chronic medications the pharmacist recommended to discontinue, cost savings were calculated using the Lexicomp published average actual wholesale price (AWP) for the medication dosage form the patient was receiving. The specific calculation is listed below:

Monthly quantity of specific formulation x AWP per unit = monthly cost savings

Excluded interventions for the cost savings analysis included medication incompatibilities with medical devices, such as inappropriate medication administration through enteral tubes. Discontinuation of PRN medications was also excluded from the cost savings analysis given the inability to estimate a projected monthly use.

Readmission Analysis. Perfecting Peds began conducting CMM in these complex pLTCF patients in August 2022. By January 2023, the team had been making substantial accepted interventions for five months and had obtained CPA consent from >95% of families/guardians. We selected to compare hospital readmissions during January–March 2022 to January–March 2023 as the historical control period in 2022 was devoid of pediatric clinical pharmacist intervention and allowed for comparison of similar time frames given the seasonality of hospital readmissions (e.g., respiratory virus season).

Results

Pediatric clinical pharmacists consulted on a total of 102 individual pLTCF patients during the 9-month study period. These patients were new to the clinical pharmacist and included an initial comprehensive pharmacist workup of drug therapy per protocol as well as monthly follow-up reviews.

Table 1 demonstrates the demographic and health care variables. The average age of patients was 13 years and 58.9% were male. Non-white patients accounted for 72% of the population, with over 50% black or African American. Median length of stay was 7.7 years.

Table 1. Patient Demographic, Conditions, and Length of Stay in Facility Variables

Patient baseline characteristics	
Number of patients	102
Female, n (%)	44 (41.1)
Male, n (%)	63 (58.9)
Age, mean in yr (range)	13 (0–30)
Race, n (%)	
Asian	2 (1.9)
Black or African American	55 (51.4)
Hispanic or Latino	19 (17.8)
White or Caucasian	30 (28.0)
Hawaiian or Pacific Islander	1 (0.9)
Complex chronic conditions	
Mean (range)	9.5 (3–15)
Medications per patient	
Mean (range)	23 (11–39)
Length of stay in facility, days	
Median (range)	2,815 (75–9723)

Table 2. Complex Chronic Medical Condition Categories and Subcategories Involving ≥ 10% of Patients and Associated ICD-10 Codes

Complex Chronic Medical Condition Category	Most Common Subcategories (≥ 10% of 102 patients)	N (%)	ICD-10 Code(s)
Neurologic or Neuromuscular	Epilepsy or epileptic spasms	83 (81)	G40
	Congenital malformations of the nervous system	58 (57)	Q00.0–Q07.9
	Cerebral palsy	57 (56)	G80
	Cortical blindness	39 (38)	H47.619
	Encephalopathy	33 (32)	G93.40, G93.49
	Hypoxic ischemic encephalopathy or anoxic brain injury	29 (28)	P91.60, P91.68, G93.1
	Persistent vegetative state	28 (28)	R40.3
	Neuromuscular dysfunction of bladder	21 (21)	N31.9
	Autonomic dysreflexia	20 (20)	G90.1, G90.4, G90.8, G90.9
Cardiovascular	Congenital cardiac malformations (except PDA, ASD, VSD)	22 (22)	Q20–Q26, I34–I37
Respiratory	Chronic respiratory failure	66 (65)	J96.1, J96.2
	Asthma	29 (28)	J45
	Congenital malformations	28 (28)	Q30–Q34
	Chronic obstructive pulmonary disease	18 (18)	J44.1, J44.9
Gastrointestinal	Chronic constipation	83 (81)	K59
	Gastroesophageal reflux disease	77 (76)	K21
	Dysphagia	73 (72)	R13
Oral cavity	Disturbances of salivary secretion	22 (22)	K11.7
Endocrine/Metabolic/Bone	Bone diseases	19 (19)	M81, M85
	Adrenal/parathyroid/pituitary dysfunction	16 (16)	E20, E21, E23.0, E24.0, E25.0, E26, E27.1
	Bone and joint anomalies	13 (13)	Q75–Q78
Chromosomal abnormalities and congenital anomalies not mentioned elsewhere	Other congenital anomalies	23 (23)	K44, Q10–Q18.9, Q79, Q86.8, Q87, Q89
	Chromosomal anomalies	13 (13)	Q90–Q99

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect

Each patient had an average of 9.5 complex chronic medical conditions. The severity and complexity of these patients is presented in Table 2. Notably, more than 80% of patients had a diagnosis of epilepsy. Additionally, these patients had a substantial dependence on technology, with 65% of all patients having a tracheotomy with ventilator dependence and 100% of patients requiring enteral feeding tubes.

Medication burden was also substantial in this population. At the beginning of the study period, each patient was receiving an average of 23 chronic medications. This number decreased by 15%

Table 3. Drug Therapy Problems (DTPs) Requiring Intervention (See Table S1 for Definitions and Descriptions)

Drug Therapy Problem (DTP)	N (%)
Dosage too low	353 (26.1)
Inappropriate/inadequate administration instructions	209 (15.4)
Inappropriate/unnecessary therapy with risk	158 (11.7)
Inappropriate/unnecessary therapy without risk	148 (10.9)
Needs additional drug therapy	71 (5.2)
ADR monitored	69 (5.1)
ADR managed	60 (4.4)
Drug-drug interaction prevented/ managed	60 (4.4)
Dosage too high	53 (3.9)
Inappropriate dosage form	37 (2.7)
Inappropriate route	34 (2.5)
Laboratory work overdue	33 (2.4)
Frequency increase interval	30 (2.2)
Alternative therapy	25 (1.8)
Frequency decrease interval	19 (1.4)
Drug acquisition	17 (1.3)
Total	1355

ADR, adverse drug reaction

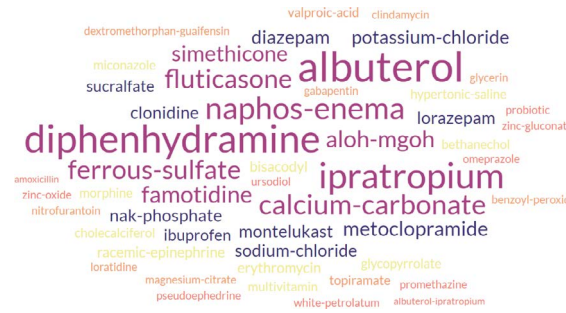
to 20 chronic medications per patient by the end of the study period.

Table 3 illustrates the clinical interventions to identify, prevent, and resolve DTPs. A total of 1355 interventions to address identified DTPs were made with an average of 13 per patient. The most common DTPs were "dosage too low," "inappropriate/inadequate medication administration details," and "inappropriate/unnecessary therapy." Definitions and examples of DTPs are found in Table S1.

A word cloud (Figure) depicts scheduled and PRN medications discontinued by the pharmacist. The most common medications recommended for discontinuation included diphenhydramine, albuterol, sodium phosphate enema, ipratropium, calcium carbonate, fluticasone, aluminum hydroxide-magnesium hydroxide, famotidine, simethicone, sucralfate and metoclopramide.

A description of the types of monitoring plans implemented by pharmacists after acceptance of pharmacist-driven clinical interventions is presented

Figure. Word cloud for discontinued medications.



AlOH-MgOH, aluminum hydroxide and magnesium hydroxide; NaK-phosphate, sodium and potassium phosphate; NaPhos-enema, sodium phosphate enema

Table 4. Types of Monitoring Plans Implemented After Pharmacist Intervention Acceptance

Types of Monitoring Plans	N (%)
Anti-epileptic drug management	95 (19.8)
Monitor bone health	93 (19.4)
Electrolyte management	79 (16.5)
Reflux management	71 (14.8)
Ensure iron absorption	51 (10.6)
Manage anticholinergic side effects	40 (8.4)
Antibiotic stewardship	18 (3.8)
Endocrine management	15 (3.1)
Maintain behavioral health	15 (3.1)
Ketosis maintenance	2 (0.4)
Total	479

in Table 4. Pharmacists implemented monitoring plans after 479 interventions. The most common types of monitoring plans included antiepileptic therapeutic drug monitoring, metabolic bone health optimization, electrolyte management, and gastroesophageal reflux management.

Actual occurrence of ADRs necessitating plan modifications (e.g., "ADR managed" category) were identified by pharmacists in 60 individual episodes. The most common ADRs identified were constipation from glycopyrrolate, hypotension and/or bradycardia secondary to clonidine, laboratory value alterations due to concomitant administration of calcium carbonate, ferrous sulfate, and/or potassium phosphate or with levothyroxine, and diarrhea/nausea/vomiting from sodium citrate. A full report of these ADRs with interventions and outcomes is found in Table S2.

The pharmacoeconomic analysis included 244 interventions for preventable ADRs. Monthly cost avoidance was calculated at $48,835 ($479 per patient per month) and included the avoidance of 28 ED visits/admissions and 61 clinic and urgent care visits. Monthly direct cost savings were calculated at $44,304 ($434 per patient per month). Total monthly total cost savings plus cost avoidance was $93,140 ($913 per patient per month). Hospital readmission data comparing January–March 2022 to January–March 2023 revealed a 44% readmission reduction from 30 to 17 readmissions.

Pharmacist recommendations had an acceptance rate of 98%.

Discussion

This is the first study, to the authors' knowledge, that uses a CPA to provide CMM to CYSHCN-CMC in a long-term care setting.

Creation of CMM via a CPA has been described by Benavides et al[43] including a methodology for the establishment of pediatric medication therapy management services due to the rising prevalence of chronic diseases in children, including various thresholds for patient eligibility based on a chronic disease profile and medication burden.[43] Pharmacist provision of CMM or medication therapy management has been a standard of care in the elderly population in LTCF for decades, endorsed by Medicare, but these services are lacking in the pLTCF population despite literature supporting such a need.[22]

Feinstein and Orth[32] discussed provider- and system-level recommendations to improve medication safety in CYSHCN-CMC. At the point of care, they suggest generation of the best possible medication list, increasing the ease of medication administration, and defining targets to measure treatment success. At the systems-level, integrated pharmacist support to provide CMM, technology and telehealth-based education and observation, and improved adverse event surveillance. In a retrospective, randomized, proof-of-concept study conducted within a large pediatric primary care clinic, Marquez et al[22] identified common drug therapy problems in 100 patients, including drug use without an indication, non-optimized or duplicate therapy, undertreated symptoms, adverse drug events, and clinically significant drug-drug interactions. We found similar drug-related needs and problem categories in this pLTCF CYSHCN-CMC population. Each of these studies provides a blueprint for the creation of durable CPAs through a standardized process for care provision and documentation afforded by CMM.

The medical conditions endured by the patients within this pLTCF illustrate the magnitude of complexity among the pediatric patient population residing within long term care facilities and highlight the need for interprofessional collaboration and coordination among the health care team for medication management given their intricacies and vulnerability. Drug-drug interaction risk is 2.5 times higher in children with more than 3 complex chronic conditions compared to those without.[30] Our patients each experienced an average of 9.5 complex chronic conditions which further illustrates their complexity and risk.

Literature supports that the risk of ADRs increases in these complex patients with increasing numbers of medications, with a threshold of 5 medications.[25] Our patients were on many more medications (average 23 per patient) and experienced varying degrees of ADRs necessitating plan modifications, including life-altering events like calcineurin-inhibitor induced nephrotoxicity from sirolimus. While our team was able to intervene on 60 ADRs directly attributed to a specific medication (as determined by our team in consultation with the medical staff and consultant specialists), there were many potential ADRs observed in patients that could not be solely attributed to one offending agent, especially when the patient's disease state compounded that risk. The numbers of these adverse events were not included in our analysis which makes our reported ADR numbers falsely low.

In an observational study, Solano et al[44] described the impact of pharmacist medication review and identified inappropriate drug administration (32.3%), herb-drug interactions (24.6%) and dose selection (17%) as the most frequent DTPs. Indeed, our most common DTPs included inappropriate drug administration and incorrect dose selection, but our patients experienced a high incidence of inappropriate/unnecessary therapies. This does not surprise the authors given that each of these patients are cared for over many years by various consultative services based outside the pLTCF. Medications are added to these patients' pharmacotherapeutic profiles during hospital admissions or by consulting specialists but not altered for years at a time due to hesitancy to change something a provider did not add themselves or due to concern for disrupting a disease state that otherwise appears stable. This is a great opportunity for pharmacists to coordinate discussions amongst the providers at the pLTCF and the consultant specialists to recommend a trial period to come off a medication or tapering plans.

Pharmacist discussions with consultant specialists (e.g., Neurology, Endocrinology, etc.) are quite important in determining the history of a specific medication for a patient, especially when trying to eliminate potentially unnecessary medications to reduce medication burden, decrease adverse events and reduce medication regimen complexity. Medication regimen complexity in CYSHCN-CMC with polypharmacy has been studied by Feinstein et al.[27] A Medication Regimen Complexity Index (MRCI), comprised of 3 sub-scores for dosage form, dose frequency, and specialized instructions, was utilized to identify potentially modifiable factors associated

with suboptimal therapies. They found a median (IQR) of 6 (4–7) dosage forms per patient, 7 (5–9) dose frequencies per patient, and 5 (4–8) instructions per patient, with significantly higher counts among higher MRCI groups.[27] With a baseline of 23 individual medications with varying dosing schedules, the patients cared for in our study exceed these numbers greatly, demonstrating their medication regimen complexities. The higher the complexity, the higher the rate of medication error and ADR.[45]

Medication burden was substantial in our cohort of pLTCF patients with a baseline average of 23 medications each. Our pediatric pharmacist team was able to decrease medication burden by 15% (3 medications per patient) in the initial 9-month pilot period, but we fully believe that as we work more closely with the prescriber group and implement medication-related protocols, this percentage will continue to grow.

The number of medications in CYSHCN-CMC has also been associated with hospital readmission.[35] Nearly one-fifth of children with at least one complex chronic condition had one or more readmissions within 30 days of discharge and readmission risk was significantly associated with being discharged home on 8 or more medications. Again, with an average of 23 medications each, our pLTCF patients' risk of readmission is quite high. Reducing the medication regimen complexity by discontinuation of unnecessary medications may influence readmission, but these studies have not been completed in the pLTCF population.

The most common discontinued medications were those on shortage, conserving use for patients who truly require the medication, or medications with known adverse effects in the pediatric population (e.g., anticholinergics, sodium phosphate enema, etc.). Many patients suffered from a heavy burden of anticholinergic symptoms such as constipation and urinary retention. It is also known that sodium phosphate enemas can cause death in patients under the age of two years.[46] Metoclopramide carries a black box warning for tardive dyskinesia, especially when used in excess of 12 weeks.[47] All of the metoclopramide discontinuations occurred in patients who had been on the therapy for years, and discontinuation did not result in any adverse events. Even more substantial interventions occurred including redesigning multiple antiepileptic pharmacotherapy plans due to adverse events and management of immunosuppressant regimens.

Yung et al[37] reported that pharmacist interventions in managing/preventing adverse drug events in a pediatric ambulatory care clinic resulted in an estimated cost avoidance of $307,210 for 212 interventions. Interventions included drug interactions, prevention or management of adverse drug events, prevention or management of drug allergies, or drug not indicated. Similarly, in a study of pharmacist interventions in pediatric oncology and hematology patients, Kim et al[48] reported that from 2361 interventions of 381 children with cancer, a cost-benefit ratio of 1.45:1 for the hospital perspective and 1.55:1 for the patients' perspective was estimated. Prevention of clinically significant adverse drug events was also reported in this study. Our study showed a substantial combined cost savings and cost avoidance at over $1,000,000 a year, certainly high enough to justify a full-time pharmacist salary in this setting which had a national average of $132,750 per year in 2022.[49]

Additional cost-reducing measures surrounding hospital readmission are a major focus of payers. After the 2012 implementation of the Hospital Readmissions Reduction Program by the Centers for Medicare and Medicaid services, many organizations implemented strategies and programs to reduce readmission rates but were mostly directed at Medicare beneficiaries and for specific conditions.[50–55] Of the pediatric initiatives launched, most were limited to inpatient readmissions from home and likely did not account for patients who had a readmission from a pLTCF, rehabilitation/transitional care hospital or medical home.[56]

While the overall number of pediatric admissions in the United States has decreased, the percentage of admissions for children with complex chronic conditions has increased, especially within the 30 days after hospital discharge.[57] This is not surprising given that children with chronic disease are living longer and developing long-term consequences of their diagnoses and are more likely than other children to be readmitted after an acute care hospitalization.[57–59]

Our study evaluated readmission incidences in CYSHCN-CMC residing at a pLTCF, which has not been previously reported in the literature. Readmissions decreased by 44% year-over-year during a similar time frame after a CPA for CMM was implemented. This further shows the benefits of pediatric-trained pharmacists in the pLTCF setting.

Opportunities to improve the quality of health care delivered and thereby promote better health outcomes for long-term care CYSHCN-CMC patients may lie in the practice's leadership in implementing data-driven processes for population health management.[60] These processes will include:

- Development of quality improvement initiatives to promote systematic change across the practice and organization;
- Implementation of academic detailing on focused drug topics;
- Creation of clinical decision support to promote best practices; and
- Identification of targeted clinical interventions, for example, vaccination promotion and optimization.

During the 9-month pilot, our pharmacists became heavily involved in the pharmacy and therapeutics committee, weekly behavioral health rounds, antibiotic stewardship, pharmacogenomics, clinical decision support, drug shortages, educational opportunities, and

failure modes and effect analyses, of which all provide the opportunity to improve the quality of health care for these patients. In addition, pharmacist completion of prior authorization requests on behalf of the physician addressed and/or removed drug acquisition barriers often present within the CYSHCN-CMC population due to the need for medications which may be utilized off-label, but necessary for appropriate care provision.[61]

A notable strength of this study is the diversity of the patient population. As mentioned previously, 72% of the patient population consisted of non-white patients. This is significant as the disparities in care that ethnic minority patients experience are well-documented in literature. For example, during the COVID-19 pandemic it was reported that black CYSHCN had greater odds of unmet mental health care, and that black and Hispanic patients had a higher unmet need for care from a specialist.[62] Our study may suggest that clinical pharmacists could help bridge health care equity gaps in this vulnerable population.

Additional strengths include that this is the first study to report many outcomes including the impact of pediatric clinical pharmacist interventions in a pLTCF and characteristics surrounding patients in pLTCF (e.g., hospital readmission data, characterization and quantification of complex chronic disease states, number of daily chronic medications, etc.).

This study had various limitations in addition to its single-study design. ADRs were grossly underestimated, particularly those where a pharmacotherapy plan revision was not specifically implemented. There were many other potential ADRs not included where the medications and disease state were likely both contributing, but a plan modification could not be made. Future evaluations could include all grades of ADRs, though utilization of causality assessment tools for ADRs in pediatric patients has demonstrated many limitations.[62,63] We did not quantify the number of off-label medications being utilized in this patient population and we did not calculate the MRCI, both of which could have been helpful for further characterizing the complexity of these patients and the risk they face for error and adverse drug event.

Another limitation is this study specifically followed the methodology of Yung et al,[37] and therefore did not report the direct cost savings or avoidance for most pharmacist interventions which resulted in an underestimate of true cost savings/avoidance. Cost avoidance from interventions such as inappropriate selection of dosage form certainly resulted in a cost avoidance as they prevented adverse events and suboptimal management (e.g., ciprofloxacin suspension binding via gastrostomy tube or inappropriate dilution of cannabidiol with gastrostomy tube administration could result in decreased availability of the drug and resultant adverse patient outcomes), but these were not included given the previous study's methodology. Furthermore, for direct cost savings, the prices of pharmacy compounded liquid solutions were based off published compounding recipes and therefore may vary from the actual price and does not account for compounding fees. Moreover, given the brevity of this pilot program, hospital readmission data was only evaluated over a 3-month period year-over-year. A lengthier and more extensive analysis of hospital readmission including readmission reasoning (e.g., medication-related adverse events versus viral illness) is warranted.

Conclusions

We present a prospective case series using a standardized process (CMM) for CYSHCN-CMC patients through a CPA. The use of a CPA to conduct CMM in CYSHCN-CMC decreased medication burden, mitigated, and prevented adverse events, reduced expenditure, decreased readmission rates and was well accepted and implemented in collaboration with pLTCF providers. Opportunities for improvement in the delivery of clinical care for CYSHCN-CMC are numerous and pediatric-trained pharmacists are well-suited for the job.

Article Information

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. Heather Monk Bodenstab is an employee of Sobi, a pharmaceutical company, but Sobi provided no support for this study or publication of this article. Jena Quinn, Heather Monk Bodenstab, and Emily Wo had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Ethical Approval and Informed Consent. Mercer University Institutional Review Board has reviewed and approved this study (H2302033) in accordance with the 2018 Federal Regulations 21 CFR 56.110(b) and 45 CFR 46.110(b) (for expedited review). The study was conducted in accordance with the Declaration of Helsinki. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. As our patients cannot provide consent either due to age or disability, all parents/caregiver(s) provided informed consent at enrollment.

Acknowledgments. The authors thank physicians, advanced practice providers, and nurses at the long-term care facility (that wish to remain anonymous) for their assistance. The authors also thank the families and caregivers for their willingness to participate, and Catherine Kuhn, PharmD, for her expertise and input.

Submitted. June 27, 2023

Received. November 8, 2023

Supplemental Material. DOI: 10.5863/1551-6776-29.2.119.S1
DOI: 10.5863/1551-6776-29.2.119.S2

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