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Original Research

A pilot study assessing the frequency and complexity of methadone tapers for opioid abstinence syndrome in children discharged to home

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Abstract

Background: Methadone is often prescribed as a taper schedule to prevent/treat opioid abstinence syndrome (OAS) or neonatal abstinence syndrome (NAS).
Objective: The objective of this study was to determine the percentage of children discharged home on methadone tapers and to develop, assess, and implement an instrument for measuring the complexity of the methadone regimens.
Methods: This study used a descriptive retrospective design to examine patients younger than 18 years from January 1, 2008, to December 31, 2008, administered methadone for prevention/treatment of OAS/NAS and discharged home on a methadone taper. Data collection included demographics and characteristics of methadone regimen. The primary objective was to determine the percentage of children discharged on methadone. Secondary objectives included characterization (ie, number of dosage and interval changes), duration, and complexity of the methadone taper. Descriptive statistics were performed using Stata v10 (StataCorp LP, College Station, TX). Complexity was evaluated using the medication taper complexity score (MTCS) between 4 raters. Reliability of the MTCS was established using interrater correlation analyses of the regimen complexity scores.
Results: Thirty-three patients (41.8%) were discharged on methadone. The median (range) age was 0.42 (0-12) years, with most patients (75.8%) initiated on methadone for prevention of OAS. Thirty-one patients were included for further analysis of medication complexity. The median (range) duration of the home taper was 8 days (2-48), which included a median (range) of 4 (1-11) dose changes and at least 1 (0-2) change in the interval. MTCS ranged from 7 to 42, with the tool demonstrating 95% interrater reliability.
Conclusions: More than one-third of patients were discharged home on methadone. The median taper duration was 8 days and included a median of 5 adjustments in either the dose or interval. The MTCS demonstrated very good interrater reliability to measure wide variability in the complexity of individual

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tapers. Future studies should determine the construct validity of the MTCS and the applicability of this tool for further research and clinical application.

Keywords: Children; Methadone; Opioid withdrawal

Introduction

Opioid abstinence syndrome (OAS) is a general term for the signs and symptoms that occur after abrupt cessation of opioids. The symptoms occur following the development of physiologic dependence after prolonged use of opioids. In children, OAS can occur in the critically ill who are exposed to prolonged sedative and analgesic agents (ie, iatrogenic OAS) and in neonates after maternal narcotic use (ie, neonatal abstinence syndrome [NAS]). Iatrogenic OAS occurs in 35% to 57% of critically ill children exposed to opioid continuous infusions (CIs).[1-3] In contrast, NAS occurs in approximately 55% to 94% of neonates exposed to opioids or heroin *in utero*.[4] The clinical presentation and management of iatrogenic OAS and NAS are identical, but the etiology of exposure differs. OAS symptoms fall into 3 separate categories including central nervous system irritability (eg, anxiety, agitation, grimacing, sleep disturbance), gastrointestinal dysfunction (eg, vomiting, diarrhea), and autonomic dysfunction (eg, tachypnea, diaphoresis, and hypertension).[5] If children are not treated properly, these symptoms could be associated with increased morbidity, prolonged hospital stay, and discomfort.[3]

Although OAS is a commonly noted complication after prolonged exposure to opioids, there is no single accepted therapy that can be used in all patients. A number of agents have been suggested including alpha-2 agonists, transdermal fentanyl, and oral morphine.[6-8] However, numerous reports have described the use of methadone because of its long half-life and ease of enteral administration (eg, tablets and oral solution) to prevent OAS symptoms.[9-19] Methadone is often administered in a tapering schedule over a period of days to weeks, based on dosing schemes obtained from published protocols. As a result of this taper schedule, some children continue to receive this agent after hospital discharge, although the frequency of this occurrence has not been specifically evaluated to date. These tapers may be complex for parents/caregivers because they often involve periodic changes to the methadone dose and dosing interval over a period of days to weeks. Because the dose of methadone in these tapers is not consistent, there is a potential that these children could be at greater risk for an administration or missing dose error. It has been identified in several studies that these 2 types of errors are the most common in the outpatient setting.[20-22] The primary objective of this study was to determine the percentage of children discharged home on methadone tapers for OAS. A secondary objective was to develop, assess, and implement an instrument for measuring the complexity of the methadone regimens.

Methods

Study design

The study used a descriptive retrospective design to examine patients younger than 18 years from January 1, 2008, to December 31, 2008, who were discharged on a methadone-tapering schedule for prevention of OAS. The study was conducted in a tertiary care, academic hospital licensed for 230 beds, including 25 pediatric intensive care units (ICUs) and 88 neonatal ICU beds. Following institutional review board approval, patients were identified through the institution's electronic database, Meditech (Medical Information Technology, Inc., Westwood, MA) if they received methadone for this indication during the designated study period. Patients were excluded if they were initiated on methadone for chronic pain indications associated with malignancies and/or palliative care. Patients also were excluded if they had incomplete medical records.

Data collection procedures

To determine the percentage of patients discharged home with a planned taper, the total number of children who were initiated on methadone therapy during the designated study period for prevention of OAS was collected. To evaluate the complexity of the home methadone taper regimens, a medication taper complexity score (MTCS) was developed by 2 investigators with

expertise in the management of OAS (P.N.J. and J.L.M.). This tool was adapted from the medication regimen complexity index (MRCI).[23] This index was developed to determine the complexity of medication regimens for adults with chronic illnesses.

Five categories were included for evaluation of the regimens on the MTCS (Fig. 1). These categories were given a weighted score based on the investigators' expert evaluation of its contribution to the overall complexity of the regimen. The total score of the MTCS could range from 7 (ie, least complex) to 50 (ie, most complex). A score of 7 would be achieved if there was not a concomitant benzodiazepine taper; in this case, the patient would receive a calculated weighted score of 0 for this specific category. Preliminary testing of the MTCS was conducted using the medication regimens of the children in this study who were discharged home on methadone. To aid this process, 2 additional practitioners with advanced pediatric pharmacy training and experience with the development of opioid tapers for prevention of OAS were recruited. All 4 pharmacists (raters) evaluated the deidentified regimens and independently scored each regimen using the MTCS.

To descriptively characterize the planned methadone tapers for children discharged to home (ie, number of dosage and/or interval changes), an attempt was made to identify the total duration of the methadone taper including a summary of inpatient and outpatient utilization. The number of unmeasurable doses also was described. This was defined as a dose less than 0.1 mL because many commercially available oral syringes cannot accurately measure these doses or was defined as a dose that cannot be measured using standard increments on an oral syringe.

Baseline data collection for each patient included the age at the time of admission, sex, hospital and ICU length of stay, and their major diagnosis at the time of admission (eg, postoperative surgery/trauma, sepsis and septic shock, pulmonary disease, NAS, other). To capture the history of prior sedative and analgesic exposure for those children with iatrogenic OAS, the recent history of opioid analgesics and concomitant sedatives (eg, ketamine, benzodiazepines, dexmedetomidine, and pentobarbital) were collected. The specific data pertaining to the fentanyl CI dosage regimen included cumulative dose of fentanyl (mcg/kg), peak rate of fentanyl CI (mcg/kg/h), duration of CI (days), and dose (mcg/kg/h) immediately before the initiation of methadone. For patients who may have received other opioid analgesic agents, the dose of their current opioid was converted to fentanyl and recorded (ie, 10-mg morphine given IV/intramuscularly [IM] = 0.1 mg of fentanyl given IV/IM).

For neonates who were diagnosed with NAS, additional data were also collected. An attempt was made to collect maternal narcotic exposure

Category	Weighted score	1	2	3	4	5
Number of methadone dosage and/or interval changes	2	0-2	3-5	6-8	9-11	≥12
Ease of measurement of methadone[a]	2	0-2	3-5	6-8	9-11	≥12
Number of methadone daily doses	2	Once daily dosing throughout the taper	<3 d of 2 or more doses	<5 d of 3 or more doses and 3-4 d of 2 or more doses	<5 d of 3 or more doses but ≥5 d of 2 or more doses	≥5 d of 3 or more doses
Duration of methadone taper (d)	1	0-5	6-10	11-15	16-20	>20
Concomitant use with benzodiazepine taper	3	None[b]	Overlap of diazepam and methadone taper of 1-5 d	Overlap of diazepam and methadone taper of 6-10 d	Overlap of diazepam and methadone taper of 11-15 d	Overlap of diazepam and methadone taper of >15 d

[a]This was defined because a dose less than 0.1 mL as many commercially available oral syringes cannot accurately measure these doses or was defined because a dose that cannot be measured using standard increments on an oral syringe. Each individual unmeasurable dose was defined because a separate event.
[b]If no benzodiazepine was administered, then the patients received a score of "0" for this parameter.

Total score: _____

Fig. 1. Medication taper complexity score.

from the electronic and written medical records. For children with NAS or iatrogenic OAS who were discharged home, the specific details of the methadone dosage regimen including initial methadone dose, duration of methadone taper, number of dosage changes, and number of interval changes were collected.

Analysis plan

Descriptive statistics were performed using Stata 10 (v10.1) (StataCorp LP, College Station, TX).[24] MTCS were considered to be continuous data. Agreement between individual scores of the raters from the MTCS was assessed for reliability using interrater correlation analyses. To evidence predictive validity of the MTCS, a 1-way analysis of variance (ANOVA) was conducted between taper regimens categorized as easy, medium, and difficult. ANOVA post hoc analyses were conducting via Bonferroni tests to help control for error slippage. For all analyses, the *a priori* level of significance was $P \leq .05$.

Results

Patient demographics

Ninety-seven patients were identified (Fig. 2). Eighteen patients were excluded because of use of methadone for chronic pain or incomplete medical records. A total of 79 patients received methadone for treatment or prevention of OAS. Forty-six children (58.2%) were eliminated from the study because they completed their taper in the hospital (n = 35), expired before they were discharged (n = 6), or were discharged to a long-term care facility (n = 5). Thirty-three patients (41.8%) were discharged home on methadone and included in the analysis of the primary objective.

Table 1 shows relevant characteristics of the 33 patients informing the study. Twenty-five children

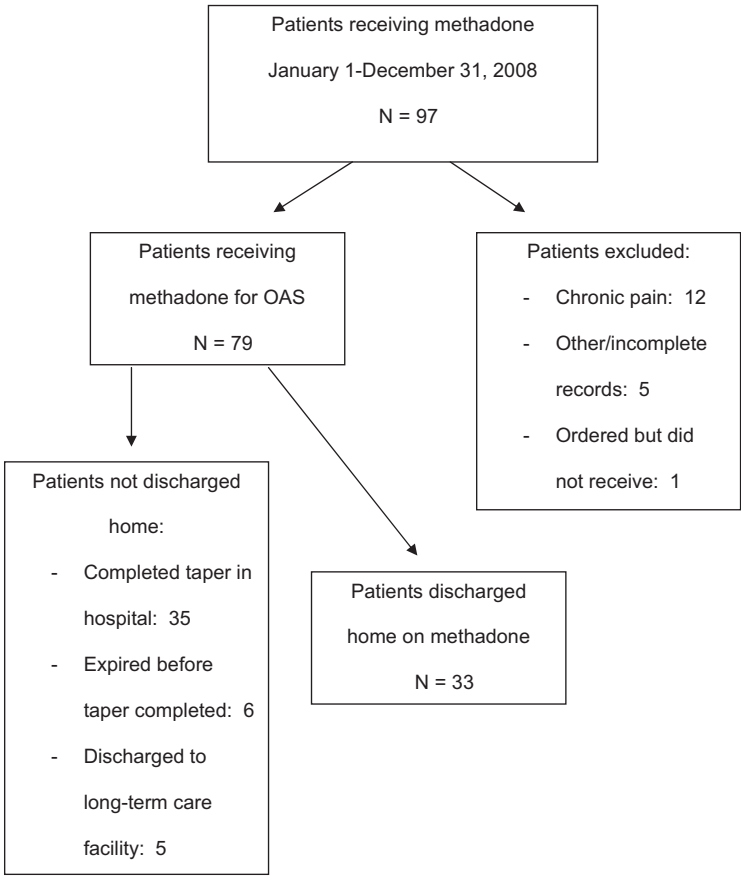

Fig. 2. Sample selection process.

Table 1
Patient characteristics (n = 33)

Variable	Median (range)
Age (y)	0.42 (0-12)
Length of stay (d)	25.6 (6-69)
Weight (kg)	11.9 (2.5-54.5)
Variable	**Total (%)**
Males	22 (66.7)
Diagnoses	
Postoperative surgery/trauma	11 (33.3)
Pulmonary disease	12 (36.4)
Septic shock/infection	4 (12.1)
NAS	3 (9.1)
Other	3 (9.1)

(75.8%) were initiated on methadone for prevention of iatrogenic OAS, and 5 children (15.1%) were initiated on methadone for treatment of iatrogenic OAS. Three neonates (9.1%) were initiated on methadone for management of NAS. There was a wide discrepancy in age noted among the patients with a median age of 0.42 years. Twenty-two patients were males (66.7%).

In the 3 infants with NAS, methadone was initiated soon after birth. All 3 infants were full-term infants. They were exposed to a variety of different agents including transdermal fentanyl (n = 1), hydrocodone/acetaminophen (n = 1), and methadone (n = 1). The maternal opioid dosages were not recorded.

Table 2 contains the demographic data of fentanyl CI in 22 of the 25 children who were initiated on methadone for prevention of iatrogenic OAS. The medical records were unavailable for the other 3 children's prior sedative/analgesic regimens. Overall, there was variability in fentanyl CI exposure as evidenced by the wide range in their peak dose, cumulative dose, and total duration of their fentanyl CI.

Five children were initiated on methadone for treatment of withdrawal associated with iatrogenic OAS. All 5 of these children received fentanyl CI. Three of the children received a concomitant midazolam CI, whereas 1 child received concomitant midazolam and dexmedetomidine CIs. Three of these children had their fentanyl CIs tapered off and were noted to have symptoms of withdrawal within 72 hours of fentanyl discontinuation. In each case, the patients were initiated on an initial dose of methadone and discharged on a taper. The other 2 children were initiated on a transdermal fentanyl patch for prevention of withdrawal after discontinuation of their fentanyl CI. Despite the use of transdermal fentanyl, the children continued to experience signs and symptoms of withdrawal and were subsequently initiated on enteral methadone to achieve more optimal control of their symptoms. After stabilization, they were discharged home on a methadone taper.

Description of methadone tapers

Thirty-one children were included in the secondary analyses. Of the 33 patients included in the analysis for the primary objective, 2 were excluded because the planned methadone taper was not available. Table 3 includes a summary of the planned methadone tapers. The reduction in dose and the interval selection were prescriber dependent. The median initial methadone dose (range) was 8 mg/d (0.12-120), or 0.88 mg/kg/d (0.05-4.1), with the majority (78.8%) receiving this in 4 divided doses. All patients were prescribed methadone oral solution (1 mg/mL). Six patients (19.4%) had at least 1 dose that was unmeasurable during the course of their taper

Table 2
Continuous fentanyl infusion demographic data (n = 22)[a]

Variable	Mean ± SD	Median (range)
Cumulative dose (μg/kg)	1474.8 ± 1535.5	730.3 (230-5751.7)
Peak dose (μg/kg/h)	6.2 ± 4.3	4.8 (1.7-14.6)
Duration (h)	292.6 ± 162.1	245.1 (90-661)
Dose before discontinuation of fentanyl (μg/kg/h)[b]	1.8 ± 1.5	1.0 (0.5-6.9)
Duration of overlap (h)[c]	69.7 ± 101.8	21.5 (11.7-379.1)

SD, standard deviation.

[a] Represents data from the fentanyl CI records of 22 of 25 children who were initiated on methadone for prevention of iatrogenic OAS.

[b] Dose administered just before discontinuation of fentanyl CI.

[c] Number of hours that the patient received both the opioid CI and methadone before discontinuation of the opioid CI.

Table 3
Summary of planned methadone tapers (n = 31)[a]

Variable	Median (range)
Initial methadone dose	
Mg/kg/dose	0.29 (0.04-1.2)
Mg/kg/d	0.88 (0.05-4.1)
Ending methadone dose	
Mg/kg/dose	0.032 (0.003-0.096)
Mg/kg/d	0.039 (0.003-0.174)
Taper duration (d)	
Total duration	21 (9-51)
Home duration	8 (2-48)
Dosage changes	
Total changes	8 (3-19)
Home changes	4 (1-11)
Dosing interval changes	
Total changes	3 (0-7)
Home changes	1 (0-2)

[a] The planned taper in 2 children who were discharged on methadone for prevention/treatment of iatrogenic OAS or NAS was unavailable.

(ie, dose less than 0.1 mL). The total median duration was 21 days, whereas the median home taper duration was 8 days.

The planned taper had a number of dosage and interval changes. The median number of dosage changes was 8 with a median of 4 dosage changes that were planned to occur once the child was discharged. Changes in dosage interval were also assessed; the median number of interval changes throughout the total duration of the taper was 3. However, the median number of interval changes after discharge was only 1. The median ending methadone dose (range) was 0.2 mg/d (0.01-3) or 0.039 mg/kg/d (0.003-0.174), with the majority (74.2%) receiving this dose once daily.

Eighteen children (58.1%) also were initiated on a concomitant diazepam taper while in the hospital. Twelve patients (38.7%) were discharged on a diazepam taper. Overall, the planned tapers for diazepam were much shorter for diazepam than methadone tapers, with a range of 1 to 12 days. The diazepam taper was not assessed in one of the patients because the taper duration was not documented in the medical record. Most of the tapers involved alternated tapering of the diazepam and methadone dose.

Methadone taper complexity assessment

Table 4 lists the MTCS from the 4 raters. Use of the MTCS took an average of 5 minutes or less per patient for each rater. The range of scores obtained from the raters was 7 to 42 for the patients in this cohort. Four regimens were noted to have a difference of greater than 5 points on the MTCS between the lowest and highest scores (ie, regimens 12, 19, 23, and 24). Using the correlation analyses to determine interrater reliability, the average interitem covariance was found to be 48.5, with a resultant reliability coefficient of 0.975. Given this cohort, the MTCS was found to have an interrater reliability of greater than 95%.

Predictive validity was assessed via a 1-way ANOVA of the scores from each of the raters averaged across 3 categories of difficulty, ranging from easy to difficult. Easy regimens were those with an average MTCS from 7 to 12.9 (n = 8 regimens). Medium regimens were those with an

Table 4
Pediatric pharmacist rankings with MTCS

Regimens[a]	Rater 1	Rater 2	Rater 3	Rater 4	Average score
1	7	9	7	7	7.5
2	23	25	25	25	24.5
3	27	27	27	27	27.0
4	26	28	28	26	27.0
5	12	12	12	12	12.0
6	16	16	16	16	16.0
7	21	21	21	21	21.0
8	25	25	25	23	24.5
9	9	9	9	9	9.0
10	18	16	18	16	17.0
11	9	9	10	9	9.3
12	29	29	39	31	32.0
13	24	24	24	24	24.0
14	13	13	13	13	13.0
15	21	21	26	21	21.0
16	11	11	11	13	11.5
17	16	16	16	16	16.0
18	8	8	10	8	8.5
19	31	32	42	20	31.3
20	22	20	22	22	21.5
21	9	9	10	9	9.3
22	25	24	28	24	25.3
23	24	24	17	30	23.8
24	9	15	15	15	13.5
25	17	17	17	17	17.0
26	11	11	11	11	11.0
27	16	16	16	16	16.0
28	16	16	16	16	16.0
29	13	13	13	13	13.0
30	13	13	13	13	13.0

[a] Data include the ratings from 30 regimens. One patient's regimen was excluded from the analysis because the total duration of benzodiazepine taper could not be determined.

average MTCS of 13 to 22.9 (n = 13 regimens). Difficult regimens were those with an average MTCS of ≥23 (n = 9 regimens). The ANOVA was used to contrast average differences between the categories of regimen difficulties. A statistically significant difference (conducted via Bonferroni post hoc analyses) was detected between all 3 groups (easy, medium, and difficult regimens).

Discussion

This is the first study to specifically describe the planned outpatient methadone regimens used for prevention and treatment of OAS. In a previous study, Tobias[11] reported on the successful management of children with OAS who received methadone after hospital discharge. However, the author provided general guidelines for tapering but did not provide an actual description of their outpatient regimen. In the present study, the complete regimen was assessed including the number of dosage changes, interval changes, and duration of taper. This study also included a novel assessment of the complexity of the planned home taper.

It is not an uncommon practice for children with OAS to be discharged on methadone. Eleven published abstracts, studies, or case reports evaluating the use of methadone for prevention or treatment of iatrogenic OAS are included in the literature.[9-19] The authors of 8 of these reports have described whether their patients were discharged home on methadone.[9-16] Sixty-five (35.5%) of a total of 183 patients were discharged home on methadone in these studies. It must be noted that none of these studies specifically addressed neonates who were initiated on methadone for management of NAS.

In the present study, approximately 42% of our patients were discharged home on methadone. A significant variation between patients for the taper duration and number of interval and dosage changes was noted. The median duration of methadone at home was approximately 1 week; however, some patients were discharged home with a planned taper duration of over a month. Additionally, a median of 5 interval or dose changes was planned. Furthermore, an attempt was made to assess the number of patients who received at least 1 dose that was determined to be unmeasurable when using a conventional oral syringe. Six patients (19.4%) had at least 1 dose less than 0.1 mL.

The variation in the regimens in this patient cohort necessitated an evaluation of the complexity of the regimens. To do this, a novel scoring tool (ie, MTCS) was developed. The MTCS was adapted from a previous study evaluating the MRCI. In their study, George et al[23] found that the 65-item MRCI was a reliable tool to evaluate the complexity of medication regimens in adults with chronic illnesses. The MTCS included 5 different categories to assess complexity including duration of taper, number of dosage and interval changes, concomitant benzodiazepine tapers, and ease of measurement (Fig. 1). This tool was developed based on insights from medication error studies in pediatric patients and the author's clinical experience. Each category was given a weighted score based on its perceived contribution to the overall complexity of the regimen. It was proposed that the concomitant use of a benzodiazepine taper along with a methadone taper would represent the most complex medication regimen. Although there are no present studies that support this assumption, patients receiving tapers with both agents may be receiving different doses and greater number of administration times compared with children receiving a methadone taper alone.

There was some additional rationale behind the development of the weighted score of the MTCS. The number of dosage and/or interval changes, ease of methadone measurement, and number of methadone doses per day had an equivocal weighted score because the author's opinion was that all of these factors could increase the likelihood of medication errors. Based on previous studies evaluating measurement of liquid medications using an oral syringe, approximately one-third to two-thirds of parents and/or caregivers were unable to accurately draw up the prescribed dose without training.[20,21] Walsh et al[22] evaluated medication errors in children with chronic illnesses and found 61 errors of a total of 280 medications reviewed. They found that approximately half of the errors were associated with missing doses and administration errors. When parents and/or caregivers were not provided the proper dosing devices, they often administered an incorrect dose. With these instances, they noted that the parents and/or caregivers were not aware of these errors and did not report them to their child's physician.

All patients in this study received oral methadone solution, but there was no documentation regarding parent and/or caregiver education for the measurement with oral syringes. With the number of dosage changes noted in this patient

cohort, there is a potential for increased error to occur because the dose was not consistent throughout the planned taper. In the authors' experience, most outpatient pharmacies carry 3 or 5 mL oral syringes. Six patients had at least 1 dose that was less than 0.1 mL. With the 3- or 5-mL syringes, it is very difficult to accurately measure this volume. In addition to these factors, the number of doses per day could increase the likelihood of taper complexity. Based on the report by Walsh et al,[22] the increased number of doses per day may lead to inadvertent omission of doses.

There are several limitations to this study. First, the data for the methadone taper were collected retrospectively. The planned methadone taper was obtained from each patient's discharge summary. There was no way to verify that the regimen was not changed by the patient's primary care provider or if a parent and/or caregiver adjusted their child's regimen independently of their child's physician. In addition, there was no way to determine if a medication error occurred during the home methadone tapers. Next, this cohort includes a small sample size. However, this sample size is consistent with previous studies that have reported the number of children discharged on methadone. To evaluate the complexity of the medication regimen, the MTCS was developed. Although the MTCS has not been fully validated, this scoring tool was adapted based on a previous study evaluating the MRCI and was determined to be highly reliable.[23] Additionally, the weighted scores of the MTCS were based on pediatric medication error studies. Only 4 of the taper regimens had raters' scores that differed by more than 5 points. On further review, it appears that these scoring discrepancies were attributed to individual rater scoring errors. For example, the rater misunderstood the planned taper and evaluated the complexity of the entire taper instead of the planned home taper. Additionally, 2 raters forgot to evaluate the concomitant benzodiazepine taper. Despite these discrepancies, the overall measure still demonstrated an interrater reliability exceeding 95%.

As previously discussed, the MTCS is not yet validated. However, this tool has the potential for application for the clinical setting and future research. First, the MTCS could be used by clinicians before discharge to identify children who are receiving complex medication tapers and would require modification of the planned taper or a targeted education session for parents and/or caregivers. For some children, their taper may be inherently complex for a variety of reasons and may not be able to be adjusted. Therefore, education is vital to make sure that parents and/or caregivers understand the regimen and are capable and comfortable to administer the planned doses. The MTCS also could be used by researchers to provide an objective measurement of complexity. There is a paucity of data concerning parent and/or caregiver perceptions of factors that increase the complexity of their child's home medication taper. This tool could be used to correlate the parents' and/or caregivers' perceptions of complexity with the calculated MTCS. However, before these studies are conducted, the MTCS must first be validated.

Conclusions

This study found that approximately 42% of children prescribed methadone for prevention and/or treatment of OAS were discharged to home on a taper regimen. The median taper duration was 8 days and included a median of 5 adjustments in either the methadone dose or interval. Applying the MTCS to this cohort, the complexity scores ranged from 7 to 42. The MTCS demonstrated very good interrater reliability and initial predictive validity. Future studies should evaluate the construct validity of the MTCS and its role as an objective measurement of complexity for medication tapers.

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