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SYSTEMATIC REVIEW

The use of methadone to facilitate opioid weaning in pediatric critical care patients: a systematic review of the literature and meta-analysis

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What is already known

- Critically ill pediatric patients are at high risk of developing opioid tolerance and experiencing iatrogenic withdrawal.
- Methadone is commonly employed to facilitate discontinuation of continuous opioid therapy and to treat withdrawal in this population.

What this article adds

- This systematic review summarizes the best available evidence from published clinical research studies to guide methadone therapy in critically ill pediatric patients at risk for iatrogenic opioid withdrawal.

Keywords
methadone; opioid substitution treatment; substance withdrawal syndrome; pediatric; pediatric intensive care; systematic review

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Summary

Background: Continuous opioid infusion therapy is commonly utilized in the pediatric intensive care setting to treat pain and facilitate tolerance of invasive therapies. Transitioning to methadone is one common strategy for weaning from continuous opioid infusions, but in practice this transition can be challenging, and many children still experience iatrogenic withdrawal.
Aim: We reviewed the literature to evaluate the best available evidence to guide methadone therapy in this setting, and to summarize associated adverse events.
Methods: We included all studies of methadone used to facilitate weaning from continuous opioid infusions in pediatric critical care patients, including medical, cardiac, and surgical patients, excluding case reports and studies treating neonatal abstinence syndrome, or acute or chronic pain. Medline, Embase, and CINAHL databases from inception to May 2015 were queried; references of included works and conference proceedings were also reviewed. Two authors independently extracted data from each study. Meta-analysis with fixed- and random-effects models was used to pool results of studies when applicable.
Results: Twelve studies involving 459 patients met criteria for inclusion. A wide variety of methadone dosing and taper strategies were reported. Mean inpatient methadone taper times varied widely, from 4.3 to 26.2 days. Excessive sedation was the most frequently reported adverse event, occurring in up to 16% of patients. Withdrawal occurred in 27% of patients among studies reporting this outcome. In three of three studies in which a new methadone protocol was introduced, a decreased proportion of patients experienced

withdrawal (standardized mean difference, SMD = −0.60, 95% CI = −0.998 to −0.195, $P = 0.004$).
Conclusion: We did not identify sufficient evidence to recommend any particular methadone weaning strategy, or to recommend methadone over other medications or prescribed infusion weaning, for successful weaning of continuous opioid infusions in the pediatric intensive care setting.

Background

The common use of opioid infusions in pediatric critical care exposes patients to potential adverse effects, including the risk of iatrogenic withdrawal when the infusion is discontinued. Withdrawal causes well-described adverse effects, including physiologic stressors such as fever, respiratory distress, tachycardia, hypertension, and feeding difficulties, as well as neurologic sequelae including agitation, hallucinations, and seizures, ultimately prolonging hospital stay (1,2). In a recent large randomized controlled trial (RCT) of pediatric intensive care unit (ICU) nurse-directed sedative management, 27% of patients in the usual-care arm had any Withdrawal Assessment Tool-1 (WAT-1) score consistent with withdrawal; 9% required additional treatment (3), suggesting a substantial burden of withdrawal with typical weaning management in current practice.

In adult intensive care, methadone has been used successfully to facilitate narcotic weaning, reducing the duration of opioid infusion (4) and the length of exposure to mechanical ventilation in specific populations (5,6). Transitioning to a long-acting opioid such as methadone is a generally accepted approach to narcotic weaning in pediatric patients (7). In a recent, large study, 30% of pediatric patients receiving usual-care sedation management for acute respiratory failure received methadone (3). Pharmacologic data support this approach. Methadone pharmacokinetics for pediatric and neonatal patients are similar to adults, and its excellent oral bioavailability and long half-life allow very stable serum levels with intermittent dosing (8), including simple once-daily oral regimens.

Despite common use, it is not well-established what dose, transition, or weaning regimen is optimal for any particular patient. In the study referenced above, among patients who required opioid re-escalation during weaning, over 50% received methadone, yet a majority still had WAT-1 scores consistent with iatrogenic withdrawal and 85% required additional treatment for withdrawal (9), suggesting that opioid weaning with methadone therapy is not straightforward for many patients. In this setting, we reviewed the literature to evaluate the best available evidence guiding the use of methadone to facilitate continuous opioid weaning in medical, cardiac, and surgical pediatric (0–18 years of age) ICU patients, with specific focus on: the length of methadone taper, home weaning duration, adverse events, proportion of patients experiencing iatrogenic withdrawal, and length of stay. Based on this review, we additionally performed meta-analyses to test the following hypotheses: (1) The institution of a methadone protocol decreases the occurrence of withdrawal; (2) The institution of a methadone protocol decreases the duration of methadone taper; and (3) Higher dose vs lower dose methadone decreases the incidence of withdrawal without increasing adverse events.

Methods

Search strategy and study selection

LD performed the search with the assistance of library staff at Seattle Children's Hospital. Search strategy included the terms: (methadone) AND ([narcotic OR opioid OR morphine OR fentanyl OR hydromorphone] AND [taper OR wean OR prolonged OR chronic OR withdrawal]) AND (pediatric) AND (critical OR intensive). This search was conducted on Medline, Embase, and CINAHL databases. An additional search using MeSH terms was performed: ICUs, Pediatric & Substance Withdrawal Syndrome/*drug therapy. An ancestry approach evaluating references cited in the identified studies and in major review articles was also performed to identify additional studies for possible inclusion. There were no restrictions on time period applied; the earliest identified case report on the topic was in 1990, and the search included publications through May 2015. We included neonatal studies if methadone was used for the purposes of weaning continuous opioid therapy but excluded neonatal studies of methadone for the treatment of neonatal abstinence syndrome (withdrawal following *in-utero* narcotic or methadone exposure). We excluded case reports, studies of methadone for the treatment of acute or chronic pain, studies focused on outpatient methadone weaning programs, and studies of methadone use to treat acute or chronic pain. Outcomes of interest included: inpatient and outpatient durations of methadone weaning, total narcotic exposure duration,

adverse events (including excessive sedation, naloxone use, and QTc prolongation), and withdrawal events (including proportion experiencing withdrawal symptoms, proportion requiring opioid rescue therapy, or change in withdrawal scoring). We also recorded, when available, the protocol, prescribed and effective doses of methadone used in each study, hospital length of stay, ICU length of stay, and any other adverse events. We included both observational studies and RCTs. Only articles in English were evaluated.

Study identification and selection is summarized in the PRISMA flow diagram in Figure 1 (10,11). Seventeen titles (15 articles plus 2 conference proceedings) met criteria based on abstract review. On full-text review, three were excluded as case reports (12–14), one was excluded for focus on outpatient weaning (15), and one was excluded for focus on outpatient combined opioid and benzodiazepine weaning (16). Twelve studies (10 articles plus 2 conference presentations) met criteria and formed the basis of this systematic review and meta-analysis. Characteristics of these 12 studies are reported in Table 1.

Assessment of study quality

The quality scoring of the 10 included nonrandomized studies was performed according to the Newcastle–Ottawa Scale, as recommended by the Cochrane Handbook (Appendices S1 and S2) (17). The score was qualitatively interpreted as high, intermediate, or low for each study if the score was above, at, or below the median score among these 10 included studies, respectively. The quality scoring assessment of the two included randomized studies was based on the Cochrane Quality Assessment Tool (Appendix S3) (17). The study quality assessments for the 12 included studies are summarized in Table 2.

Data extraction

Articles were independently coded by LD and BY, according to prespecified criteria (Appendix S4). Each article was evaluated regarding: the population studied; the duration and dose of opioid infusion prior to methadone initiation; the comparison groups and the comparisons performed; exposure and outcomes information (see Background, above); and study quality (see Assessment of study quality, above). Both coders were initially blinded as to each other's coding. After coding studies independently, the coders compared their coding results to ensure interrater reliability on coding methodology. Coders resolved disagreements by jointly reviewing discrepancies with reference to the original paper; no unresolvable disagreements occurred.

To select articles for meta-analysis, the 12 studies identified above were grouped by comparability of exposures and comparability of outcome data reported, in order to select studies appropriate for meta-analysis. Meta-analysis of a specific exposure–outcome relationship was performed when at least three studies were identified with similar exposure and a similar outcome measure reported. All studies with compatible exposure and outcome data were included.

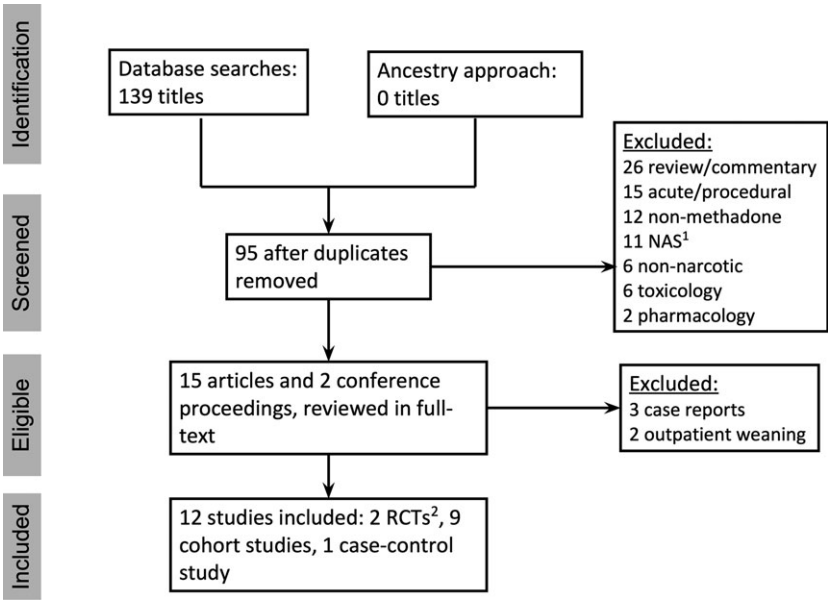

Figure 1 Flow diagram indicating the number of studies identified, screened, assessed for eligibility, and included in this systematic review and meta-analysis. [1]Neonatal abstinence syndrome. [2]Randomized controlled trial.

Table 1 Characteristics of 2 Interventional Studies and 10 Observational Studies Concerning Methadone and Narcotic Weaning in Pediatric Critical Care Patients

Author and year Interventional studies	*n*	Study type	Intervention	Outcomes assessed
Berens 2006 (24)	37	Randomized trial	5 day vs 10 day methadone taper	Withdrawal score; # rescue doses; LOS
Bowens 2011 (26)	78	Randomized trial	Low (weight-based) vs high (fentanyl-based) methadone dosing	Proportion completing a 10-day taper; withdrawal symptoms; dose increase

Author and year Observational studies	*n*	Study type	Comparison group	Outcomes assessed
Robertson 2000 (29)	20	Retrospective and prospective cohorts	Pre- vs postprotocol	Time to taper; withdrawal symptoms and treatment; delayed taper
Lugo 2001 (23)	22	Retrospective cohort (postprotocol)	No dose increase vs dose increase required	Time to taper; opioid overlap; withdrawal symptoms; opioid exposure; LOS
Meyer 2001 (25)	29	Prospective cohort (postprotocol)	Withdrawal vs no withdrawal on 10-day taper	% completing assigned taper
Siddappa 2003 (27)	30	Case–control analysis within retrospective cohort (postprotocol)	Withdrawal vs no withdrawal; Receiving <80% vs >80% dose predicting withdrawal	Methadone dose; ROC analysis of dose predicting withdrawal Withdrawal
Basnet 2011 (22)	26	Retrospective cohort	Pre- vs postprotocol	Methadone and lorazepam dose; time to taper; withdrawal; LOS
Jeffries 2012 (34)	43	Retrospective cohort	Low opioid exposure vs high exposure	Methadone dose; time to taper; withdrawal score; dose increase; LOS
Johnson 2012 (28)	55	Retrospective cohort	Low (<median) vs high (>median) methadone dose	Methadone dose; associations with opioid exposure, withdrawal and dose changes; time to taper; LOS
Lista 2013 (35)	37	Retrospective cohort	None	Withdrawal score; rescue doses
Giby 2014 (30)	30	Retrospective cohort	Short vs medium vs long methadone taper	Methadone weaning patterns and dose in different phases; opioid exposures; opioid overlap; time to taper
Steineck 2014 (31)	52	Retrospective cohort	Pre- vs postprotocol	Time to taper, rescue doses, opioid overlap, withdrawal score, LOS

LOS, length of stay; ROC, receiver operator characteristic. Withdrawal reported variously as: withdrawal symptoms, withdrawal symptoms requiring treatment (withdrawal treated), and withdrawal scoring.

Statistical analysis

STATA SE 12 with free-license meta-analysis add-on software was used for all analyses (18). Analyses were conducted with respect to the standardized mean difference (SMD) with 95% confidence interval (19). Both the chi-squared and *I*-squared statistics were used to assess study heterogeneity (20). Fixed-effect meta-analyses were performed for all analyses, except when significant heterogeneity was found, in which case analyses for both fixed and random effects were performed and reported. To combine results of studies reporting median (range) data, we used previously published techniques to estimate mean (± standard deviation, SD) (21).

Results

Study design and variability

The 12 included studies involved a total of 459 pediatric intensive care patients in whom methadone was used to facilitate weaning from a continuous opioid infusion. There was substantial heterogeneity in population and in drug exposure prior to methadone therapy. Two studies included only ventilated patients (22,23), while others excluded ventilated patients (24,25) or included them only if they successfully extubated within 72 h of initiating methadone (26,27). Some studies included only patients in whom methadone was used for treatment of withdrawal (25), while others specifically excluded such

Table 2 Quality assessment coding of 12 included studies

	Interventional studies												
	Concealed group assignment	Intention to treat analysis	Blinded outcome assessment	Groups comparable at entry	Subjects blinded	Providers blinded	Equal other care	Defined inclusion/exclusion criteria	Defined intervention	Defined outcome	Appropriate clinical period	Total score	Quality[a]
Berens 2006 (24)	0	2	2	1	2	2	2	2	1	2	2	18	High
Bowens 2011 (26)	2	1	1	1	2	1	0	2	1	1	1	13	Int

	Cohort studies									
	Representativeness of exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome not present at study start	Comparability of cohorts	Outcome assessment	Adequate length of follow-up	Adequacy of follow-up	Elements present (/9)	Quality[b]
Robertson 2000 (29)	*	*	*			*	*		5	Int
Lugo 2001 (23)	*		*	*		*	*		5	Int
Meyer 2001 (25)		n/a	*		n/a	*	*	*	4	Low
Basnet 2011 (22)	*	*	*				*	*	5	Int
Jeffries 2012 (34)	*	*	*			*	*	*	6	High
Johnso n 2012 (28)	*	*	*	*	*		*	*	7	High
Lista 2013 (35)	*	n/a	*		n/a	*	*		4	Low
Giby 2014 (30)	*	*	*	n/a		*	*		5	Int
Steinec k 2014 (31)	*		*				*		3	Low

	Case–control study								
	Adequate case definition	Case representativeness	Control selection	Control definition	Comparability of cases and controls	Exposure ascertainment	Equal ascertainment for cases and controls	Assessment of nonresponse	Elements present (/9)	Quality[b]
Siddappa 2003 (27)	*	*	*			*	*	*	6	High

[a]Each item is scored using the following scale: 2 = adequate and well described; 1 = partially adequate or partially described; 0 = inadequate or not described. The total quality score for each study is the sum of the individual item scores for that study. Maximum score = 22. Scoring: high quality = 18–22; intermediate quality = 13–17; low quality ≤12.

[b]Comparability is scored to a maximum of 2, yielding a possible total of nine positive elements. Translation to a qualitative score (high, intermediate, low) is based on a study's number of positive elements being above, at, or below the median score (of five positive elements) among those included in this review.

*Element present, as described by the Newcastle-Ottawa Scale (Appendices S1 and S2)

patients (28). Five of 12 studies included only patients exposed to fentanyl; one included only patients exposed to morphine. The six studies including patients exposed to a variety of opioids reported all exposures as fentanyl equivalents. The four studies specifying a conversion factor calculated fentanyl equivalents as 10 μg fentanyl = 1 mg morphine = 0.15 mg hydromorphone (28–31). Opioid exposures prior to methadone therapy ranged more than 17-fold, from a mean cumulative fentanyl dose of 590 $\mu g \cdot kg^{-1}$ (26) to a cumulative fentanyl dose of 10 500 $\mu g \cdot kg^{-1}$ for one patient (27). In all studies, patients received additional sedative medications; no study excluded patients receiving medications that may have impacted withdrawal symptoms or opioid weaning (e.g. clonidine or ketamine). Several studies included a simultaneous benzodiazepine taper with their protocol for methadone weaning (23–26).

Methadone dose and taper regimens were also heterogeneous, and are summarized in Table 3. Initial methadone doses ranged from 0.15 to 1.8 $mg \cdot kg^{-1} \cdot day^{-1}$. Higher doses were typically based on opioid infusion dose at the time of methadone initiation; when derived from the previous opioid infusion dose, initial methadone doses ranged from 1 to 16.7 times the daily fentanyl dose (in $mg \cdot kg^{-1} \cdot day^{-1}$) (22,26,29). A 6-h initial dose interval was most common (8/12 studies), as was initial oral dosing (10/12 studies). Two studies initiated IV methadone for all patients (27,29); others offered IV methadone as an option, given at 1/2 to 1/3 the calculated oral dose (30,31). Studies that employed a higher methadone : fentanyl conversion rate at a 6-h interval often used that regimen as a 'loading dose', and reduced the dose substantially on day 2 or 3 (26,29). The period of overlap between initiating methadone and discontinuing the opioid infusion ranged from one to four days and, in one study, correlated with the duration of fentanyl infusion and the cumulative dose (23). The specifics of infusion wean within this time frame were infrequently reported, but ranged from reducing the fentanyl infusion from 10% (23) to as much as 50% (27) every 8 h during the overlap period.

Methadone and the development of iatrogenic withdrawal

Five of 12 studies employed a validated tool to assess withdrawal. Tools used included the Neonatal Abstinence Score (Finnegan score), the WAT-1, and institution-specific modifications of these tools (32,33). Six additional studies reported withdrawal in terms of nursing-reported physiologic symptoms; five of these six studies were published before the WAT-1 score was available (prior to 2008). Six of 12 studies reported using a standardized approach to managing withdrawal; all employed rescue morphine doses, with or without an additional methadone dose (24), increasing the baseline methadone dose (27), and/or delaying the taper (23,29). No study directly compared a methadone strategy to an alternative strategy for opioid discontinuation (e.g., scheduled opioid infusion weaning, clonidine therapy). However, two studies made specific effort to investigate effective methadone doses (26,27). One study developed an ROC curve to explore the methadone dose–withdrawal relationship and determined that a daily methadone dose of at least 2.5 times the total daily fentanyl dose was associated with reduced withdrawal, in a patient population exposed to 4–117 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of fentanyl for 7–41 days. A dose less than this had an odds ratio of 21 for developing withdrawal (27). An additional study randomized patients to a weight-based dose vs a fentanyl-based dose; the risk ratio for developing excessive withdrawal in the fentanyl-based dose (higher dose) group compared to the weight-based group was 0.5 (26). A separate regression analysis demonstrated cumulative and peak opioid doses to be independently associated with the methadone dose ultimately required (28).

Methadone taper length and length of stay

The most common methadone taper strategy was a taper over 10 days following successful discontinuation of the opioid infusion, transition to oral dosing, and/or tapering to a 12- or 24-h dose interval. Taper strategies ranged from 3% to 20% methadone dose reduction per day; some strategies employed larger weans less frequently (e.g., 25% every 2–3 days (23)). Actual taper times varied widely and had little relationship to the taper strategies; mean taper times ranged from 8.1 to 18.2 days among studies with a 10 day taper strategy. However, in the two studies utilizing a taper strategy based explicitly on previous opioid exposure, actual taper times were within intended times (31,34). In the study focused on weaning patterns, longer tapers were observed at higher opioid exposures (30). Several studies excluded patients discharged home during the methadone taper (30,31,35) or did not obtain follow-up, limiting conclusions regarding true total methadone taper time. Five studies reported hospital length of stay (average ranging from 19 to 37 days (22–24)), and four studies reported PICU length of stay (average ranging from 15 to 36 days (28,31)). One additional study reported a reduced hospital length of stay following implementation of a protocol from 109 to 67 days (31).

Table 3 Methadone dosing and opioid infusion discontinuation

	Group description	Opioid exposure, days opioid infusion	Methadone dose ($mg \cdot kg^{-1} \cdot day^{-1}$, or infusion-based)	Initial dose interval (h)	Methadone dose received, 1st 24 h[a] ($mg \cdot kg^{-1} \cdot day^{-1}$)	Overlap with infusion (days)[b]	Taper strategy	Total taper days	Proportion developing withdrawal	Study comments
Interventional studies										
Berens 2006 (24)	5-day taper	11.4 ± 5.3		12	0.5 ± 0.1		20% daily	31% > 5 days	19%	Randomized patients already transitioned to methadone to two taper strategies
	10-day taper	15.5 ± 10.7		12	0.6 ± 0.1		10% daily	24% > 10 days	19%	
Bowens 2011 (26)	Low (weight-based) dose	8.8 (6.3–12.9), combined	0.4	6		3	10% daily		26%	Interpretation complicated by study data reporting by success vs failure of taper, instead of assigned treatment group
	High (infusion-based) dose		16.7* TDDF[c]	6	*1.24*	3	10% daily		15%	
Observational studies										
Robertson 2000 (29)	Preprotocol	11 (8–19)						20 (9–31)	30%	Methadone dose/taper protocol; excluded patients d/c home during taper
	Postprotocol	15 (7–53)	16.7* TDDF[d]	6			5 or 10 days	9 (5–10)	20%	
Lugo 2001 (23)	No withdrawal (no dose increase)	17.8 ± 8.4, combined	0.4 (*6*TDDF*)	6	0.5 ± 0.2	2.7 ± 1.9	14–18 days	18.2 ± 11.9, combined	0%	Methadone and lorazepam dose/taper protocol; 14% d/c home during taper
	Withdrawal (dose increase)		0.4 (*5*TDDF*)	6	0.9 ± 0.4	4.9 ± 3.9			100%	
Meyer 2001 (25)	Single cohort postprotocol	14.5 ± 9.2	10* TDDF	12	*2.3*		10% daily	86% within 10 days	10%	Methadone rescue and taper protocol, enrolled only patients with withdrawal; 55% d/c home during taper
Siddappa 2003 (27)	No withdrawal	10 (7–41)	3* TDDF, comb.	8	0.*6*	1.3, comb.	3–10% daily, comb.		0%	Case–control and ROC analysis to identify dose preventing withdrawal, after methadone and lorazepam dose/taper protocol; 30% d/c home during taper
	Withdrawal	12.5 (7–26)		8	*1.0*				100%	

Table 3 Continued

	Group description	Opioid exposure, days opioid infusion	Methadone dose ($mg \cdot kg^{-1} \cdot day^{-1}$, or infusion-based)	Initial dose interval (h)	Methadone dose received, 1st 24 h[a] ($mg \cdot kg^{-1} \cdot day^{-1}$)	Overlap with infusion (days)[b]	Taper strategy	Total taper days	Proportion developing withdrawal	Study comments
Basnet 2011 (22)	Preprotocol	11.7 ± 12.5			1.9 ± 2.2			4.29 ± 4.76	46%	Methadone and lorazepam dose/taper protocol; more days and higher doses of lorazepam, ketamine, and dexmedetomidine postprotocol
	Postprotocol	11.2 ± 2.7	1 * TDDF	12	1.1 ± 0.4	1.5	10–20% daily	8.08 ± 2.72	0%	
Jeffries 2012 (34)	Low-risk (<10 days infusion)	9 (5–24), combined	0.78 * TDDM	6	*0.6*		20% daily	9 (0–48)	42%, combined	Methadone dose/taper protocol; included only patients exposed to morphine; low total daily dose of drug exposure (mean *c.* 30 $\mu g \cdot kg^{-1} \cdot h^{-1}$ morphine)
	High risk (>10 days infusion)		1 * TDDM	6	*0.7*		10% daily	15 (7–91)		
Johnson 2012 (28)	Low (<median) dose methadone	10.5 ± 7.2	*6* TDDF*	6, 8	0.5 ± 0.2	1.4 ± 1.6	10–20% every 24–48 h	14.7 ± 9.2	40.7%	Age, cumulative fentanyl dose also differed by dose group; excluded patients with prior withdrawal
	High (>median) dose methadone	16.4 ± 13.8	*10* TDDF*	6	1.8 ± 1.0	2.8 ± 3.8		26.2 ± 11.5	42.9%	
Lista 2013 (35)	Single cohort, no protocol	9 (IQR 7–11)		6, other	*0.5*	2 (IQR 1–4)		10.4 ± 4.9		No patients d/c home during taper
Giby 2014 (30)	Single cohort, no protocol		*0.35 *TDDM*		0.5 (0.08–2.6)	2 (1–18)	15%, 9%, or 4% daily	19.8 ± 9.5		Study designed to evaluate exposure-based taper patterns; most (>70%) patients also on benzodiazepines and clonidine; excluded if d/c home during taper
Steineck 2014 (31)	Preprotocol	25% < 10 days				3.3 ± 2.3		24.7 ± 15.5		Methadone dose/taper protocol; excluded if d/c home during taper
	Postprotocol	20% < 10 days	0.15–0.8, exposure–based	6, 8		1.8 ± 1.6	3–24 days, exposure-based	15 ± 7.4		

'–', items not reported in a particular study; TDDF, total daily dose fentanyl; TDDM, total daily dose morphine. Fentanyl total daily dose is calculated in $mg \cdot kg^{-1} \cdot day^{-1}$ based on the best information available within a study: fentanyl daily dose ($mg \cdot kg^{-1} \cdot day^{-1}$) = fentanyl rate ($\mu g \cdot kg^{-1} \cdot h^{-1}$) × 24 ($h \cdot day^{-1}$) × 0.001 ($mg \cdot \mu g^{-1}$). Data reported as mean ± SD, or as median (range), except where otherwise noted. Italics denotes an estimated dose, reported without SD, calculated from other study data when available.

[a]Dose received is reported in addition to intended or prescribed dose, if available.

[b]Actual overlap reported if available. Otherwise, intended or recommended overlap (per study or protocol guidelines) is reported.

[c]Up to a maximum of 10 mg per dose (40 mg per day).

[d]Up to a maximum of 20 mg per dose.

*Indicates multiplication

Safety

Sedation was the most frequently evaluated side effect. Three studies employed a validated scale for routine evaluation of excessive sedation: the Modified Ramsey Sedation Score (24), the Modified Motor Activity Assessment Scale (26), and the State Behavioral Scale (34). Excessive sedation requiring a decrease in dose occurred in 2–16% among the three studies reporting this outcome (26,28,34). Interestingly, the higher proportion of excessive sedation occurred in the high-dose methadone group in one study (26), but in the low-dose group in another (28), underlining the contribution of existing opioid tolerance. Related to this, the study reporting the highest incidence of excessive sedation used an average dose of methadone (0.63 $mg \cdot kg^{-1} \cdot day^{-1}$), but had the lowest relative opioid exposure among the studies (0.75 $mg \cdot kg^{-1} \cdot day^{-1}$ of morphine) (34). The four studies reporting the use of naloxone reversal for excessive sedation noted infrequent use, in only three of a total of 93 subjects among the studies (22,29,34,35). No study reported on the need for re-intubation or CNS imaging secondary to excessive sedation. Only one study performed EKG monitoring and in only 5 of 43 (11.6%) patients; QTc prolongation occurred in one-fifth of these patients (34). Reported adverse effects are summarized in Table 4.

Meta-analysis

Results of the meta-analysis indicated that the institution of a methadone protocol was associated with a decreased likelihood of withdrawal in all three studies in which it was evaluated (Figure 2). There was moderate heterogeneity (I-squared = 56%, $P = 0.10$). In a fixed-effects model, the SMD was −0.60, favoring a decreased likelihood of withdrawal following the initiation of a methadone protocol (95% CI = −1.0 to −0.2, $P = 0.004$).

The institution of a methadone protocol decreased the methadone taper duration in two of three studies (29,31). There was substantial heterogeneity (I-squared = 91.7%, $P < 0.005$). In a fixed-effects model, the SMD was −0.49, favoring a reduction in taper duration following the initiation of a methadone protocol (95% CI −0.93 to −0.05, $P = 0.029$). In a random-effects model, the SMD was −0.72; this result failed to reach statistical significance (95% CI = −2.39 to 0.94, $P = 0.40$). However, for the study in which the protocol increased taper time (22), the protocol taper time was more similar to that of other studies (a mean of 8 days, up from 4.3 days in the nonprotocol arm), and the protocol led to reduced withdrawal, suggesting that the longer taper provided benefit.

Higher dose vs lower dose methadone decreased the likelihood of withdrawal in two of three studies (26,27). There was substantial heterogeneity (I-squared = 73%, $P = 0.025$). In a fixed-effects model, the estimated relative risk was 0.63, favoring reduced withdrawal with higher dose methadone therapy (95% CI 0.40–1.00, $P = 0.05$). In a random-effects model, the estimated relative risk was 0.52; this result failed to reach statistical significance (95% CI = 0.19–1.4, $P = 0.20$).

Table 4 Reported adverse effects

	n	Naloxone use	Oversedation	QTc prolongation
Interventional studies				
Basnet 2011 (22)	26	0%		
Berens 2006 (24)	37			
Observational studies				
Robertson 2000 (29)	20	1/10 (10%) preprotocol	One 10× dose error requiring reversal	
Lugo 2001 (23)	22		No dose decreases	
Meyer 2001 (25)	29		'No oversedation, desaturation, or hypotension'	
Siddappa 2003 (27)	30		'No cases of respiratory arrest'	
Bowens 2011 (26)	78		2.9% low-dose and 15.4% of high-dose group required dose held for sedation	
Jeffries 2012 (34)	43	2/43 (5%)	16% required dose held for oversedation	EKG monitoring performed in 5/43 (11.6%); 1/5 (20%) demonstrated QTc prolongation
Johnson 2012 (28)	56		14.8% low-dose and 7.1% high-dose group required dose decrease for sedation	
Lista 2013 (35)	37	0%		
Giby 2014 (30)	30			
Steineck 2014 (31)	52			

QTc, corrected QT interval.

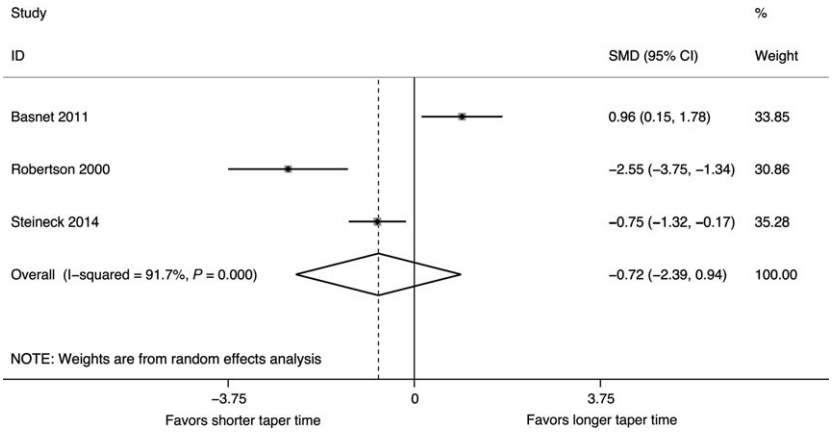

Figure 2 The effect of instituting a methadone therapy protocol on the proportion of study patients experiencing withdrawal. Square size is proportional to study sample size. Fixed-effects analysis. $n = 3$ studies. $P = 0.004$.

Discussion

Twelve studies reported a methadone strategy to facilitate weaning from continuous opioid infusions in pediatric critical care patients, and, despite marked variability among the studies, several important findings emerged. The introduction of a protocol outlining a methadone dose and taper strategy is associated with a decrease in the proportion of patients experiencing withdrawal, albeit in a limited number of studies. An individual patient's risk of developing withdrawal is consistently associated with duration of opioid therapy, cumulative dose, peak dose, and possibly exposure to fentanyl compared to other opioids (1,28,36). While some question the utility of converting current narcotic dosing to an equivalent methadone dose to prevent withdrawal during weaning (23), later studies in this series trended toward prescribing a methadone dose based on both current dose and duration of opioid exposure. Exposure-based dosing above 2.4 times the daily fentanyl exposure was associated with a reduced likelihood of withdrawal in studies designed to assess this outcome (26,27). In patients with higher previous opioid exposures, higher doses of methadone appear to be well tolerated (28,31). This literature overall also supports employing a methadone taper plan based on the individual patient's opioid exposure. Disagreement persists as to the most appropriate taper for various exposures, balancing the costs associated with longer therapy against the risk of withdrawal with rapid weaning. Given the reasonably high proportion of withdrawal present in these studies, the specific approach that will reliably prevent withdrawal, avoid oversedation, and minimize total duration of therapy remains unknown.

Prescribing a methadone dose and regimen that will minimize side effects is challenging in part due to the complexity of methadone pharmacokinetics, particularly in critically ill patients. Methadone is highly lipophilic, with a large volume of distribution; a loading dose or a long loading period is required to achieve a steady state of drug concentration (8). This results in a long, variable terminal half-life, with a broad range—7–65 h in healthy patients. Therefore, dose adjustments also take a long time to reach steady state and demonstrate clinical effect and may be less predictable in critically ill patients (37). The use of a loading regimen in our reviewed studies varied, but the benefits of a loading regimen are supported by the study examining different doses utilized in different phases of treatment (30) and by pharmacologic data estimating that a minimum starting dose of 0.2 $mg \cdot kg^{-1}$ q8 h is required to 'load' to a therapeutic methadone level (to achieve pain relief) in 36 h (8). Achieving an even higher serum level may be required to prevent withdrawal, depending on previous opioid exposure and tolerance. Although infrequently employed in the studies reviewed here, the best taper strategy is likely also exposure-dependent. Given these complexities, several published protocols involve an ICU pharmacist to support the ICU team in developing individualized dose and taper regimens (22,29,31).

The extremely limited reporting of adverse effects makes identifying a reliably safe methadone dose very difficult, particularly in light of the mandatory FDA warning regarding life-threatening QT prolongation associated with methadone therapy. Pharmacologic data suggest that maintenance methadone use is associated with an average 10 ms increase in QTc (8), so performing a screening EKG prior to therapy and a subsequent EKG during therapy, while avoiding additional QTc prolonging medications, may be the safest practice. This gap in knowledge underscores the importance of monitoring for and reporting all potentially relevant outcomes, including adverse events, in clinical research.

As noted elsewhere, safely discontinuing opioid therapy in the intensive care setting requires gradual opioid weaning (1). When such a wean is expected to be lengthy, providers can transition to oral or subcutaneous opioids, including methadone, to reduce the burden of a lengthy taper of a continuous infusion. As an alternative approach, providers can add other medications to treat symptoms of opioid withdrawal, allowing for a more rapid removal of the opioid. These pharmacologic options include buprenorphine, clonidine, dexmedetomidine, gabapentin, propofol, and propoxyphene (1). Data detailing the total costs and comparative risks of any particular approach are limited or unavailable, and no large studies directly comparing any two approaches have been performed in the pediatric population. In addition to generally favorable pharmacokinetics, allowing for once-daily oral dosing, methadone demonstrates additional pain-relieving effects through *N*-methyl-D-aspartate (NMDA) receptor antagonism and has relatively stable pharmacokinetics in the setting of hepatic and renal dysfunction, which may be advantageous in a critically ill population (37).

The limitations of this review and meta-analyses center on the difficulty of drawing useful clinical conclusions from the heterogeneous data available. Limitations also include the unlikely possibility of missing studies or other research that has been done on this topic, despite our efforts to include all published research. We did not pursue a quantitative assessment of possible publication bias due to the limited number of studies available.

Conclusions

Further studies are needed to investigate optimal methadone dosing and tapering strategies to support clinicians' efforts in effectively preventing the high burden of opioid withdrawal currently present among pediatric critical care patients requiring continuous opioid therapy. There are no studies directly comparing methadone therapy to alternative options, such as prolonged infusion taper, transition to short-acting enteral narcotics, and/or symptomatic management with clonidine. Therefore, the safest, most effective, and most cost-effective approach remains unknown. Pediatric critical care sedation practice has also evolved considerably over the 15 years in which these studies were published, as providers have increased focus on timely extubation, incorporated new sedative agents, increased use of noninvasive ventilation, and gained new knowledge regarding risk factors for the development of delirium. These shifts in sedation practice will certainly impact the epidemiology of iatrogenic withdrawal, and influence which patients will be best served by different strategies. Ideal future studies would compare methadone to alternative strategies; directly compare different methadone conversion doses; separately compare different taper strategies among patients who are otherwise at similar risk of withdrawal; utilize a standardized method for assessing withdrawal and ongoing pain; thoroughly report possible safety issues, including QTc prolongation; and include outcomes related to methadone weaning after hospital discharge. With more complete information, we can ensure that this common practice is evidence-based and most likely to achieve success, to reduce the substantial burden of opioid withdrawal as a consequence of pediatric critical care.

Ethical approval

This research did not require ethics board approval and conforms to the stated ethical standards of this journal.

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Conflicts of interest

The authors report no conflict of interest.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Newcastle–Ottawa quality assessment scale: observational studies.

Appendix S2. Coding manual for observational studies.

Appendix S3. Quality assessment scoring for randomized studies.

Appendix S4. Data coding sheets.

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