Morphine and Methadone for Neonatal Abstinence Syndrome: A Systematic Review

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ABSTRACT

Purpose: To compare the effects of morphine and methadone on length of hospital stay (LOS) or treatment (LOT) and adverse effects in infants with neonatal abstinence syndrome (NAS).
Design: Systematic review.
Sample: PubMed, Google Scholar, Cochrane library, CINAHL, IPA, American Academy of Pediatrics, and clinicaltrials.gov were systematically searched to identify randomized controlled trials (RCTs) and observational studies. comparing morphine and methadone for NAS.
Outcomes: LOS, LOT, adverse effects.
Results: One RCT, two cohort studies, and two chart reviews met inclusion criteria. Each had a low risk of bias. LOS ranged from 12.08 to 36 days with morphine and 21 to 44.23 days with methadone. LOT ranged from 7.46 to 22.9 days (morphine) and 13.9 to 38.08 days (methadone). Adverse effects were not reported. Clinical evidence comparing morphine to methadone for NAS treatment is limited and conflicting. A recommendation for one over the other cannot be made based on these outcomes.

Keywords: neonatal abstinence syndrome (NAS); neonatal withdrawal; pharmacology

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The purpose of this systematic review and analysis was to compare the effects of postnatal morphine and methadone on NAS outcomes such as length of hospitalization, length of treatment, and adverse events.

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In the United States, opioid pain relievers accounted for more than 214 million prescriptions dispensed in 2016. Rates of opioid prescribing are higher for female compared with male patients, with nearly 22 out of every 100 females filling or refilling a prescription in 2016.[1] As rates of opioid use have increased, the epidemic of opioid use and abuse has extended to pregnant women and has become a growing public health concern. An analysis of a large Medicaid claims database including records for over 1.1 million pregnant women between 2000 and 2007 found that 21.6 percent of pregnant women received an opioid prescription, with more than 28,000 women receiving more than 30 days of treatment while pregnant.[2]

Increased use of opioids during pregnancy has resulted in elevated risk to the fetus and a higher incidence of neonatal abstinence syndrome (NAS). The number of infants experiencing withdrawal symptoms because of NAS (e.g., jitteriness, tremors, diaphoresis, loose stools, poor feeding, weight loss, tachycardia, excoriations, excessive crying/irritability, and seizures), in data reported by 21 states, increased by almost 300 percent, from 1.5/1,000 hospital births in 1999 to

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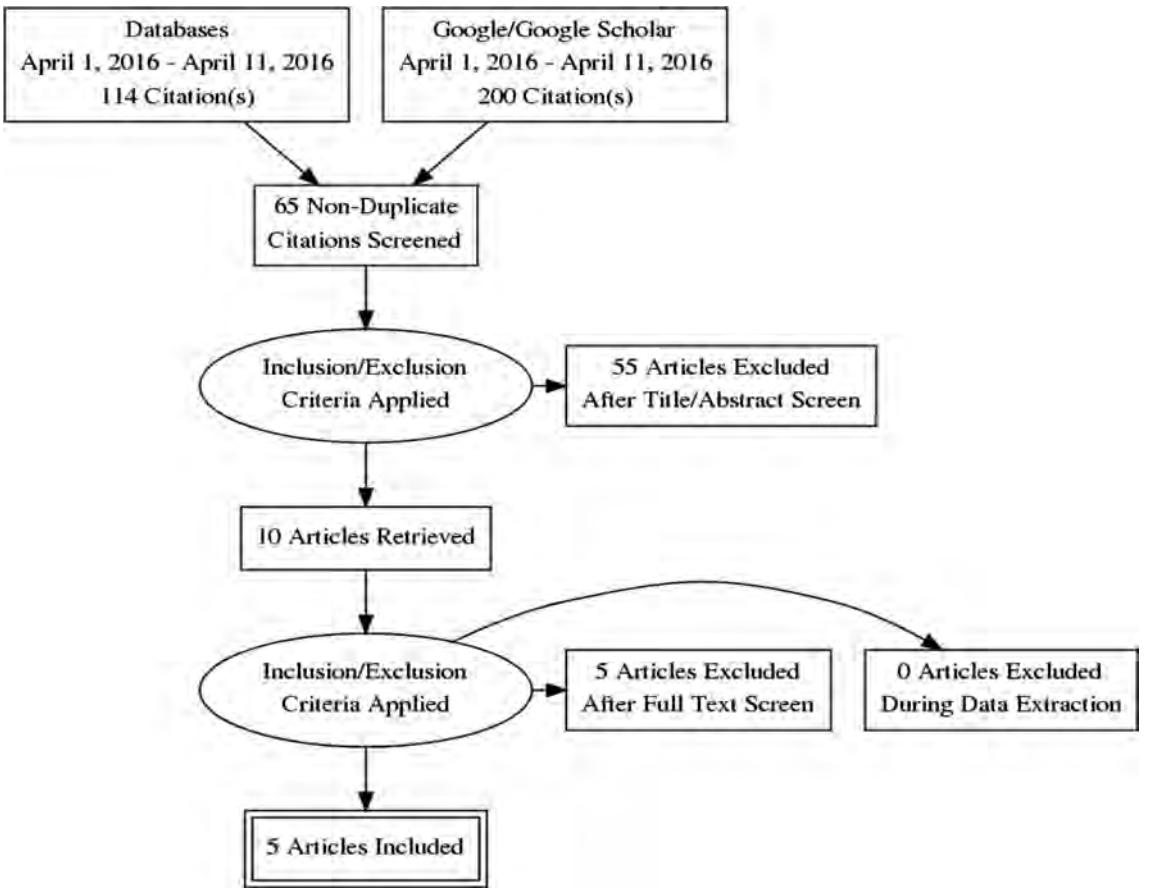
FIGURE 1 ■ Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram indicating the number of studies identified, screened, assessed for eligibility, and selected for inclusion.



6/1,000 in 2013.[3] The American Academy of Pediatrics' (AAP) Clinical Report on Neonatal Drug Withdrawal recommends pharmacologic treatment for NAS in neonates with moderate-to-severe withdrawal symptoms who have an inadequate response to nonpharmacologic treatment. The most common first-line pharmacologic treatment options are oral morphine (off-label use) and methadone, though the AAP states that there is limited evidence to recommend one agent over the other. The AAP also stresses that length of NAS treatment should be minimized because of potential detriment to mother-infant attachment, and to reduce the risk of adverse effects from postnatal opioid use.[4]

METHODOLOGY

A systematic review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1).[5] Utilizing PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Google, Google Scholar, Clinicaltrials.gov, International Pharmaceutical Abstracts (IPA), and meeting abstracts from the American Association of Pediatrics (AAP), a systematic literature search was conducted by the primary author (LS) to identify all relevant articles. The search was conducted from April 1 to April 11, 2017.

Search Strategy

The search strategy in PubMed included the following search terms: ("neonatal abstinence syndrome"[All Fields] OR "neonatal abstinence syndrome"[mh]) AND ("methadone"[All Fields] OR "methadone"[mh]) AND ("morphine"[All Fields] OR "morphine"[mh]) AND "humans"[MeSH Terms]. The search strategy in CINAHL, Cochrane Library, Google, Google Scholar, and IPA included the keywords "neonatal abstinence syndrome" AND "morphine" AND "methadone." The first ten pages of results were reviewed in Google and Google Scholar. Search terms in Clinicaltrials.gov included "neonatal abstinence syndrome" and intervention search terms were "morphine AND methadone." Search terms in AAP included the keywords "neonatal abstinence syndrome." Additional studies were identified for potential inclusion using an ancestry approach, evaluating references cited in identified studies.

Study Selection

Articles were eligible for full review and inclusion if they were randomized controlled trials (RCT), cohort studies,

case control studies, or chart reviews that were conducted on humans. Additionally, they must have compared the use of methadone and morphine to treat NAS in newborns and assessed outcomes of length of treatment (LOT) or length of hospitalization (LOH). There were no restrictions on publication date or language.

A cursory screening of article titles and abstracts was conducted by one author (LS). Obviously irrelevant search results were excluded. Following this initial screening, two authors (LS, DH) independently screened abstracts of the remaining articles to determine if they met the inclusion criteria for full review and inclusion. Disagreements were resolved by discussion.

Data Extraction

Two authors (LS, DH) independently extracted data from the included articles using a data extraction form. Descriptive data extracted from studies included study design, geographic location of study, study time period, intervention route of administration, intervention doses, concurrent use of adjunct medications in neonates, neonate gender, gestational age, prenatal drug exposure, maternal age, neonate receipt of breast milk, and "rooming in" practices. Outcomes data extracted from studies included LOH (days), length of NAS treatment (days), and adverse effects. Authors compared data and came to consensus by discussion. Study authors were contacted for missing data in the selected studies.

Assessment of Study Quality

Risk of bias assessment was conducted independently by two authors (LS, ZRC) using the Cochrane Risk of Bias tool for RCTs and the Newcastle Ottawa Scale (NOS) for nonrandomized studies.[6,7] RCTs were assessed for methodologic quality on the basis of six domains: random sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome data, incomplete outcome data, and selective reporting. Risks of bias for RCTs were described as "low risk" if they met all assessment criteria. They were described as "high risk" if they met none of the criteria or if they had one criterion or more deemed inadequate, which could significantly impact quality. A study was determined to be of "unknown risk" if there was insufficient information to make a judgment. Semiquantitative, quality assessment for nonrandomized studies using the NOS evaluated risk of bias in the following domains: selection of cohorts, comparability of cohorts, and assessment of studies' outcomes. Each quality domain was assigned one star (or two stars in the comparability domain) for a maximum total of nine stars. Based on previously published studies' use and interpretation of the NOS tool, high scores from seven to nine indicate "low risk," scores from four to six indicate "moderate risk," and scores from one to three indicate "high risk."[8–10] Discrepancies between authors were resolved by discussion and consensus.

Statistical Methods

A meta-analysis using Comprehensive Meta-Analysis (CMA) v. 3 was planned to compare the effects of morphine and methadone on LOT and LOH. A qualitative synthesis was conducted without the planned meta-analysis because of limitations of the data available across the study sample.

RESULTS

one RCT, two retrospective cohort studies, and two retrospective chart reviews were selected for inclusion in the qualitative assessment. Each study compared the use of morphine to methadone in the treatment of NAS (Table 1). The RCT included 31 participants. The retrospective chart reviews included samples of 26 and 46 participants, respectively. The retrospective cohort studies included an unknown number of participants in one article and 383 in the other. One study assessed LOT, one study assessed LOH, and three studies assessed both outcomes. There was within- and between-study variation in prenatal exposure to opioids or other legal or illicit agents. Prenatal exposure included buprenorphine, methadone, antidepressants, benzodiazepines, and others. Results for the outcomes of LOT and LOH were conflicting across studies (Table 2). LOT ranged from a mean of 7.46 to 22.9 days for infants receiving morphine and mean of 13.9 to 38.08 days for those receiving methadone. LOH for infants treated with morphine ranged from a mean of 12.08 to 21.6 days. LOH for infants treated with methadone ranged from a mean of 21.5 to 44.23 days. Two studies found a statistically significant difference in LOT, one favoring methadone[11] and one favoring morphine.[12] Morphine was also associated with a statistically significant shorter LOH in the study by Young and colleagues. In that study, morphine was dosed per protocol based on Finnegan symptom scores, whereas methadone was dosed based on weight using the Neonatal Withdrawal Inventory scoring system. No other significant differences were found among the included studies for either outcome. Adverse effects were not described as outcomes in any of the studies.

Individual Studies

Randomized Controlled Trial. An RCT by Brown and associates compared the effects of morphine and methadone with LOH in 31 infants treated for NAS between January 2011 and October 2012. This single-center, double-blind study randomized infants born to mothers who were receiving medication-assisted treatment with either methadone or buprenorphine for opioid addiction. All baseline characteristics were similar between groups with the exception of median maternal methadone dose, which was statistically significantly higher in the morphine-treated infant group than in the methadone-treated infant group (160 mg compared with 72.5 mg, respectively). Infants were treated with a standard rooming-in nursing process, and NAS symptom severity was assessed using a modified Finnegan scoring scale. Included infants were treated with oral morphine ($N = 15$) or oral methadone ($N = 16$), with starting doses of either 0.05

TABLE 1 ■ Characteristics of One Randomized Study and Four Observational Studies Comparing Morphine and Methadone in the Treatment of NAS

Author and Year	Number of Participants	Study Design and Outcomes Assessed	Morphine Dosing	Methadone Dosing	Adjunct Therapy
Brown 2015[11]	Morphine = 16 Methadone = 15	RCT; LOT	Based on modified Finnegan scores; Starting dose: 0.05 mg/kg or 0.1 mg/kg every 4 hours Dose increases: 0.05 mg/kg every 12 hours Maximum dose: 0.2 mg/kg/dose	Based on modified Finnegan scores; Starting dose: 0.05 mg/kg or 0.1 mg/kg every 4 hours Dose increases: 0.05 mg/kg every 12 hours Maximum dose: 0.2 mg/kg/dose	Clonazepam, Phenobarbital
Young 2015[12]	Morphine = 13 Methadone = 13	Retrospective chart review; LOH, LOT	Based on Finnegan scores; protocol adapted from Johns Hopkins University	Based on Neonatal Withdrawal Inventory scores; weight-based dosing; no specific protocol utilized	Clonidine, Phenobarbital
Hall 2014[13]	Morphine = 232 Methadone = 151	Retrospective cohort; LOH, LOT	Based on Finnegan scores; formalized weaning protocol (additional details not reported)	Based on Finnegan scores; formalized weaning protocol (additional details not reported)	Phenobarbital
Patrick 2014[14]	Not provided	Retrospective cohort; LOH, LOT	Not reported	Not reported	Clonidine, Phenobarbital
Lainwala 2005[15]	Morphine = 29 Methadone = 17	Retrospective chart review; LOH	Based on Finnegan scores; Starting dose: none Maintenance dose: 0.05 mg/kg/dose Dose increases: 0.03 mg/kg every 4 hours Maximum dose: 0.8 mg/kg/day	Based on Finnegan scores; Starting dose: 0.1 mg.kg/dose Dose increases: 0.025 mg/kg every 4 hours Maintenance dose: total methadone dose in previous 24 hours	Not reported

Abbreviations: LOH = length of hospitalization; LOT = length of treatment; NAS = neonatal abstinence syndrome; RCT = randomized controlled trial.

mg/kg or 0.01 mg/kg every four hours for both groups, based on symptom scores. Clonazepam or phenobarbital was administered as adjunct therapy to infants having difficulty weaning from the study medications. The median LOT was shorter with the use of methadone (14 days, interquartile range [IQR] 10,20) compared with morphine (21 days, IQR 15.8,29.5) in the treatment of NAS ($p = .008$).[11]

Retrospective Cohort Studies. A multicenter, retrospective, cohort study, involving 20 hospitals in Ohio, compared the effects of an established NAS stringent weaning protocol (SWP) with nonprotocol weaning in 547 patients from January 2012 to July 2013. Severity of NAS symptoms was assessed using the Finnegan scoring tool. Over 40 percent of infants were exposed prenatally to one or more nonopioid

TABLE 2 ■ NAS Outcomes in Included Randomized Controlled Trials and Observational Studies

Study	Morphine Length of Treatment	Methadone Length of Treatment	Morphine vs. Methadone Length of Treatment	Morphine Length of Hospitalization	Methadone Length of Hospitalization	Morphine vs. Methadone Length of Hospitalization
Brown 2015[11]	Mean: 22.9 d (*SD* 9.7) Median: 21 d (25th, 75th % 15.8, 29.5)	Mean: 13.9 d (*SD* 4.6) Median: 14 d (25th, 75th % 10, 20)	Median $p = .008$	Not provided	Not provided	Not provided
Young 2015[12]	Mean: 7.46 d (*SD* 4.88; SE 1.35)	Mean: 38.08 d (*SD* 27.38; SE 7.6)	$p = .001$	Mean: 12.08 d (*SD* 4.63; SE 1.28)	Mean: 44.23 d (*SD* 27.95; SE 7.75)	$p < .001$
Hall 2014[13]	Mean: 15.6 d (95% CI 13.0, 18.1)	Mean: 16.2 d (95% CI 12.7, 19.6)	$p = .79$	Mean: 21.6 d (95% CI 19.9, 23.4)	Mean: 21.5 d (95% CI 12.7, 19.6)	$p = .9$
Patrick 2014[14]	22.2 d	17.4 d	Not provided	25 d	21 d	Not provided
Lainwala 2005[15]	Not provided	Not provided	Not provided	Median: 36 d (IQR 33–39)	Median: 40 d (IQR 30–51)	$p = .142$

Abbreviations: d = days; IQR = interquartile range; NAS = neonatal abstinence syndrome; RCT = randomized controlled trial; *SD* = standard deviation; *SE* = standard error; CI = confidence interval.

substances, including both FDA-approved pharmacologic agents and illicit drugs, and more than 40 percent of infants were exposed to one or more nonopioid substances. A greater number of patients' mothers in the SWP group also received one or more prenatal care visits and a greater proportion of their infants were treated in the NICU, rather than a step-down or normal newborn nursery. A subgroup analysis of the study population, which included 383 infants who were treated according to the SWP with either morphine or methadone, showed no statistically significant difference in LOH or LOT between agents. However, the study may not have been adequately powered to detect this subgroup difference.[13]

A retrospective cohort study by Patrick and colleagues evaluated NAS treatment practices, including the use of morphine and methadone, at 43 children's hospitals within the United States. A total of 1,424 infants treated for NAS were included in this study, which assessed the impact that patient and hospital variables had on various NAS outcomes. In a bivariate analysis adjusting for setting, demographic variables, and consistency of treatment, methadone was associated with a shorter mean LOH (21 vs 25 days) and mean LOT (17.4 vs 22.2 days) than morphine, though there were no statistical analyses provided for these comparisons.[14]

Retrospective Chart Reviews. A retrospective chart review by Young and colleagues examined data from 26 newborns treated for NAS at a single site from September 2010 to March 2011. The mean gestational age of infants was approximately 270 days and roughly half of the infants were male. Most mothers tested positive for polysubstance abuse during pregnancy, and less than half received adequate prenatal care. Included infants were treated with oral morphine ($N = 13$) or oral methadone ($N = 13$), with different evaluation and dosing protocols for the two groups. Infants who received morphine were evaluated every four hours using the Finnegan scoring tool and received dosage adjustments starting at 0.04 to 0.12 mg of oral morphine every four hours. Infants in the morphine group also received adjuvant therapy with phenobarbital and clonidine according to protocol. Those in the methadone group were evaluated using the Neonatal Withdrawal Inventory, with no specific protocol for methadone dosage adjustments. Initial methadone dosage was weight-based and administered every 8–24 hours. The methadone group received physician-directed, weight-based adjuvant therapy without use of a specific protocol. Morphine was associated with a statistically significant decreased mean LOT (7.46 vs 38.08 days, $p < .001$) and decreased mean LOH (12.08 vs 44.23 days, $p < .001$) when compared with methadone. Those in the methadone group received a higher maximum morphine equivalent opioid dose during treatment. Infants in the methadone group received a mean maximum morphine equivalent opioid dose of 1.06 compared with 0.41 in the morphine group ($p = .001$). Additionally, there was a significant difference in the cost of the hospital visits between groups, with the visit cost being approximately three times higher in the methadone group than the morphine group.[12]

A retrospective chart review of infants treated for NAS at two Boston area hospitals between January 1997 and December 1999 compared the effect of morphine and methadone on LOH. Seventeen infants received a methadone loading dose, followed by maintenance doses with a maximum dose of 0.5 mg/kg, and 29 infants received either diluted, deodorized, tincture of opium (DTO), or neonatal morphine solution (NMS), with a maximum daily dose of 0.8 mg/kg. The Finnegan scoring scale was used to assess NAS symptoms and inform treatment dosing. Mean gestational age of the infants was 39 weeks and approximately half of the infants were exposed to more than one drug in utero. No significant difference in length of stay between infants receiving either DTO or NMS and those receiving methadone was identified, although the study may not have been adequately powered to detect a difference. However, Lainwala and associates did find that both maternal methadone dose and infant birth weight were positively correlated with LOH.[15]

QUALITY ASSESSMENT

All studies were assessed for risk of bias (Tables 3 and 4). The RCT by Brown and associates was determined to carry an overall low to unknown risk of bias, because of inadequate description of study personnel blinding and outcome assessment blinding. Additionally, a difference between groups in maternal methadone doses at baseline contributed to a high risk of bias determination in the "Other Biases" category. Each of the four observational studies were considered to carry a low risk of bias, although one study[12] did not control for between-group differences in maternal drug use and another[13] did not describe criteria excluding infants requiring opioid therapy for non-NAS indications, which may be concurrent with NAS treatment. Overall, however, the body of evidence reviewed was determined to be of high quality and at low risk for bias.

DISCUSSION

According to the AAP 2012 guidance on the treatment of NAS, methadone and morphine are considered first-line options, without evidence to support one agent over the other.[4] Despite the availability of new evidence since the AAP guidance was published, this systematic review found insufficient evidence to determine the comparative efficacy of morphine and methadone. The current body of evidence identified in this systematic review corroborates the AAP's recommendation.

Pharmacokinetic differences between morphine and methadone may represent one difficulty in comparing the two agents. Morphine's shorter half-life could make weaning titrations easier to apply, whereas methadone's longer half-life may help prevent breakthrough symptoms. Optimal weaning protocols designed specifically for each agent do not appear to be in place, which makes direct comparison between the two

TABLE 3 ■ Quality Assessment of Included Randomized Controlled Trial

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Other Biases
Brown 2015[11]	Low risk	Low risk	Unknown risk	Unknown risk	Low risk	Low risk	High risk

agents problematic. Several other limitations exist within the body of evidence comparing morphine and methadone that also hinder the ability to adequately compare the two agents. Beyond the lack of randomized trials, baseline characteristics between groups in each study and among the selected studies varied widely, making interpretation and generalization of the results difficult. Due to the nonrandomized design of four of the studies, prenatal exposure to opioids or other agents (including selective serotonin reuptake inhibitors, benzodiazepines, and illicit drugs) was not equally distributed between groups receiving morphine and methadone. Additionally, one study did not describe prenatal drug exposure. NAS symptom characterization and time to onset can differ based on the drug to which neonates are exposed in utero, and can be exacerbated by exposure to substances like nicotine, underscoring the need for more narrow inclusion criteria in future studies.[16] Formalized NAS treatment protocols were described in some intervention groups and not in others. The use of adjunct therapy also differed among studies. In some cases, a combination of methadone or morphine with clonidine, clonazepam, or phenobarbital was reported, while in another case adjunct therapy was not reported. Finally, nonpharmacologic aspects of neonatal care such as receipt of breast milk and the implementation of a rooming-in policy for mother and infant were not described in all of the studies. Variation within and between studies in each of these aspects of prenatal exposure and pre- and postnatal care could potentially confound length of NAS treatment and LOH results.

Ongoing studies comparing morphine to methadone for the treatment of NAS include two randomized trials, one open-label and one blinded, both of which primarily assess LOH. Length of opioid treatment and need for adjunct therapy, along with other patient-oriented outcomes, such as growth, will also be assessed.[17,18] Additional future RCTs are warranted to determine comparative efficacy of morphine and methadone. Prospective studies that control for prenatal drug exposure, utilize standardized weaning protocols for both agents, and optimize nonpharmacologic treatments are needed before one agent can be recommended over the other.

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TABLE 4 ■ Quality Assessment of Included Observational Studies

Study	Representativeness of Exposed Cohort	Selection of 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/ Quality
Young 2015[12]	*	*	*	*	None	*	*	*	7/high
Hall 2014[13]	*	*	*	None	**	*	*	*	8/high
Patrick 2014[14]	*	*	*	*	*	*	*	*	8/high
Lainwala 2005[15]	*	*	*	*	**	*	*	*	9/high

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