Real-world evidence to assess medication safety and effectiveness in children: Systematic Review Drugs – Real-world Outcomes

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Supplementary online content

This supplementary material has been provided by the authors to give readers additional information about their work.

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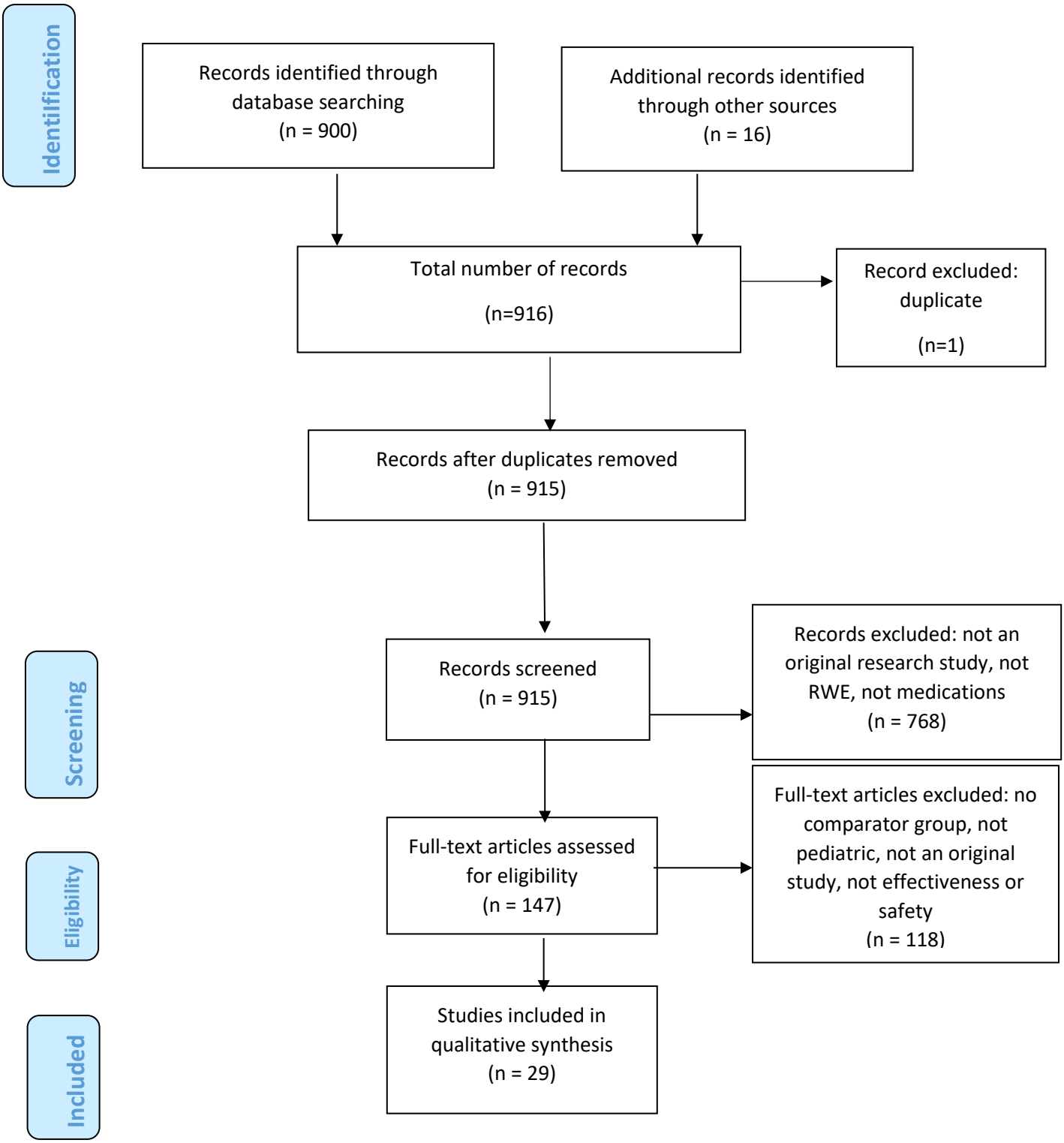
eAppendix 1. Search strategy

Search of PubMed was conducted on July 5, 2017.

Strategy	Concept	Search terms
#1	Real-world evidence	Administrative claims OR Medical records OR Databases, pharmaceutical OR Real-world OR Registries OR pharmacoepidemiology OR Comparative effectiveness research OR drug related side effects and adverse reactions OR treatment outcome OR pragmatic clinical trial OR patient reported outcome measures OR adverse effects OR long term adverse effects OR drug hypersensitivity OR pharmacogenomic testing
#2	Medications	Medications
#3	Pediatric (from Leclercq et al, 2013 (1))	(Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*
#4	#1 AND #2 AND #3	
#5	Pediatric journals (three)	((("Pediatrics"[Journal]) OR "The Journal of pediatrics"[Journal]) OR "JAMA pediatrics"[Journal])
#6	Medications	Medications
#7	#5 AND #6	
#8	Exclusions	((("Clinical Trial"[pt] OR "Editorial"[pt] OR "Letter"[pt] OR "Randomized Controlled Trial"[pt] OR "Clinical Trial, Phase I"[pt] OR "Clinical Trial, Phase II"[pt] OR "Clinical Trial, Phase III"[pt] OR "Clinical Trial, Phase IV"[pt] OR "Comment"[pt] OR "Controlled Clinical Trial"[pt] OR "Letter"[pt] OR "Case Reports"[pt] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "collected works"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "ephemera"[Publication Type] OR "guideline"[Publication Type] OR "historical article"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "personal narratives"[Publication Type] OR "pictorial works"[Publication Type] OR "practice guideline"[Publication Type] OR "video audio media"[Publication Type] OR "webcasts"[Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "double-blind"[All] OR "placebo-controlled"[All] OR "pilot study"[All] OR "pilot projects"[Mesh]))))
#9	#4 OR #7	
#10	#9 NOT #8	
Filters		Published between January 1, 2016 and December 31, 2016 English Humans

eAppendix 2. Figure S1. PRISMA flow diagram



eAppendix 3. Study Protocol

Specific Objectives

To describe the current state of RWE in pediatric pharmacoepidemiology by identifying studies published during a 1 year period (2016) that use RWE to assess effectiveness or safety of a medication in pediatric populations.

To describe the number of studies using RWE by: country, disease area, medication, pediatric age group, safety/effectiveness and type of RWE.

Criteria for including studies in review

Population

Pediatric will be defined as "under 18 years". The age of interest is the earliest age at exposure to medications studies (i.e., if patients are children when exposed and followed into adulthood to determine long term effects, the population will be considered to be pediatric). This will exclude studies where exposure takes place during pregnancy.

Interventions or exposures: Medications

All prescription medications will be included. The search strategy will not attempt to identify over the counter (OTC) medicines or other products such as vitamins or supplements. OTC medicines will be included if a study enters the pool of eligible studies, but the search strategy will not be designed to retrieve articles about OTC medicines. Studies of vaccines will not be included.

Outcomes of interest

All safety and effectiveness endpoints.

Setting

Real-World Evidence (RWE) is defined as "information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications."(2) This is interpreted to mean that a range of sources can be considered to be RWE and does not require that a study use more than one source.

Additional exclusion criteria

Published before January 1, 2016 and after December 31, 2016.
Pragmatic trials, randomized (and non-randomized) Clinical Trials.
Observational studies that assessed pharmacoeconomics and health services utilization or drug utilization (without consideration of effectiveness or safety outcomes).
Abstracts only (no full manuscripts), duplicate studies, preliminary publications.
Non-English publications.
Case studies, case series, letters, reviews (systematic and non-systematic), although systematic reviews will be hand searched for studies not retrieved by the search strategy.
Studies with exposure occurring as a fetus or exposure through breast milk.

Search methods

Studies will be identified using a three-pronged approach: 1) electronic search using search terms, 2) search of three pediatric journals for articles about medications, and 3) extended search. See supplement xx for full search strategy.

1. Electronic search for RWE and pediatric as concepts

An electronic search of PubMed using terms for the concepts of RWE and pediatric, published in 2016, in English, and in Humans only.

2. Search of three pediatric journals

An electronic search of three journals, Pediatrics, J Pediatrics, and JAMA Pediatrics, for studies of medications, published in 2016, in English, and in Humans only. These journals were selected by the authors through consensus.

3. Extended search
The references cited in reviews identified in the search will be hand searched for citations of potential relevance to the current study. Working group members will provide expert suggestions on citations that may have been missed in the other search efforts.

Screening

Screen 1. Titles and abstracts
Abstracts and titles will be screened against inclusion criteria by two reviewers. If either reviewer recommends the title for screening it will be included. Review of the titles and abstracts will be recorded on an Excel spreadsheet.

Screen 2. Full text
Full text will be retrieved for citations meeting eligibility criteria in Screen 1. Full text articles will be screened against inclusion criteria by two reviewers. Differences in assessments will be discussed by the two reviewers and adjudicated by a third reviewer if necessary. Review of full-text articles against eligibility criteria will be recorded on an Excel spreadsheet.

Data extraction of full text articles
Articles meeting the eligibility criteria in Screen 2 will be extracted using a standardized data extraction form (Excel spreadsheet). One reviewer will extract data for each article, and a second reviewer will review the extracted data.

Quality appraisal/assessment
Included studies will be assessed using the Good Research for Comparative Effectiveness (GRACE) Checklist (3).

Summary tables
Summary tables will describe the number of studies using RWE by: country, disease area, medication, pediatric age group, safety/effectiveness and type of RWE. We will report on numbers of studies, and numbers of children included in each study.

Anticipated or actual start date
March 2017

Anticipated completion date
February 2018

Funding sources/sponsors
None

Conflicts of interest
None known

eAppendix 4. Differences between study protocol and study manuscript

Section	Protocol	Final study as reported in manuscript	Reasons for changes
Criteria for including studies in the review	Described in the protocol	Additional exclusion: Studies without control or comparator groups	Additional exclusion criteria
Objectives, Summary tables	Describe type of RWE	Describe data collection approaches, data sources	Clearer and more specific than categorizing type of RWE

eAppendix 5. Data items extracted

1. Study years
2. Study population age
3. Countries where study was conducted
4. Disease or condition defining the patient population
5. Study design
6. Medication that defined exposure
7. Control/comparison group
8. Data source used
9. Name of the database
10. Statistical methods used to test study hypotheses
11. Statistical methods used to control for potential confounding
12. Linkage to parental or sibling data
13. Linkage to school data
14. Safety endpoints
15. Effectiveness endpoints

References eSupplement 1

1. Leclercq E, Leeflang MM, van Dalen EC, Kremer LC. Validation of search filters for identifying pediatric studies in PubMed. The Journal of pediatrics. 2013;162(3):629-34.e2.
2. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med. 2016;375(23):2293-7.
3. Dreyer NA, Bryant A, Velentgas P. The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness. J Manag Care Spec Pharm. 2016;22(10):1107-13.

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eSupplement 2

eTable S1. Study characteristics

Author	Country(ies) where study was conducted	Sample size in studies where study population is under 18	Age range	Disease or condition defining the patient population	Medication(s) in exposure or treatment group	Comparator/ control group	Primary safety endpoint	Primary effectiveness endpoint	Study design	Data collection
Barger-Kamate et al	Mali	307	0-10	Malaria	Artemether-lumefantrine	Unexposed or untreated	NA	cytomegalovirus shedding	prospective cohort	Manual record review and/or primary data collection
Barnard-Brak et al	U.S.	1079	6-12	Autism spectrum disorder	stimulants	Unexposed or untreated	NA	improved behavior, communication, and attention	prospective cohort	Manual record review and/or primary data collection
Barth et al	Germany	Not applicable	not reported	Juvenile idiopathic arthritis	antirheumatic drugs	Another treatment	malignant tumors	NA	case-control	Manual record review and/or primary data collection
Batton et al	USA	367	Preterm, low birth weight or healthy newborns	Preterm infants	fluid bolus (≥10 ml/kg of crystalloid), dopamine, dobutamine, hydrocortisone, epinephrine, or any blood product	Another treatment	incidence of death or neuro-developmental impairment / developmental delay	NA	prospective cohort	Manual record review and/or primary data collection
Berkenwald et al	US	Not applicable	7-18	primary nocturnal enuresis	oral desmopressin and oral oxybutynin immediate release	Different dose	No primary endpoint specified	minimum of 14 consecutive nights of complete dryness	retrospective cohort	Manual record review and/or primary data collection
Brown et al	US	544	infants	single-ventricle heart disease	digoxin	Unexposed or untreated	NA	Interstage mortality	retrospective cohort	Registry
Duerden et al	Canada	138	Preterm, low birth weight or	Preterm infants	Midazolam, also morphine and fentanyl	Different dose	Hippocampal growth	NA	prospective cohort	Manual record review and/or primary data collection

			healthy newborns							
Author	**Country(ies) where study was conducted**	**Sample size in studies where study population is under 18**	**Age range**	**Disease or condition defining the patient population**	**Medication(s) in exposure or treatment group**	**Comparator/ control group**	**Primary safety endpoint**	**Primary effectiveness endpoint**	**Study design**	**Data collection**
Gracious et al	US	50673	6-17	Depression	Antidepressants	Unexposed or untreated	Fracture	NA	retrospective cohort	Administrative claims
Horton et al	UK	9295	1-15	children with infections	systemic antibiotics	Unexposed or untreated	Psoriasis	NA	case-control	Electronic health records
Knupp et al	USA	118	0-2	Infantile spasms	Adrenocorticotropin, oral corticosteroids, or vigabatrin	Another treatment	NA	Infantile spasm remission	prospective cohort	Manual record review and/or primary data collection
Kostik et al	Russia	281	2-10	Juvenile idiopathic arthritis	Methotrexate	Unexposed or untreated	NA	prevention of uveitis	retrospective cohort	Manual record review and/or primary data collection
Li et al	China	101	not reported (mean ages of treatment groups were 3.4 and 1.9 years)	congenital heart disease	histidine-tryptophan-ketoglutarate	Another treatment	NA	reduction in mortality	prospective cohort	Manual record review and/or primary data collection
Pandya et al	UK	60	infants	Preterm infants	iron, furosemide	Unexposed or untreated	Blood acetaldehyde concentrations	NA	prospective cohort	Manual record review and/or primary data collection
Schwarz et al	US	257	0-2	infantile spasms	vigabatrin	Unexposed or untreated	visual field loss	NA	retrospective cohort	Manual record review and/or primary data collection
Scott et al	UK	21714	0-2	children with infections	systemic antibiotics	Another treatment	Obesity	NA	retrospective cohort	Electronic health records

Author	Country(ies) where study was conducted	Sample size in studies where study population is under 18	Age range	Disease or condition defining the patient population	Medication(s) in exposure or treatment group	Comparator/ control group	Primary safety endpoint	Primary effectiveness endpoint	Study design	Data collection
Sdona et al	Greece	1841	infants	Necrotizing enterocolitis	Intravenous dextrose, phototherapy, or antibiotics	Another treatment	necrotizing enterocolitis	NA	case-control	Manual record review and/or primary data collection
Shapiro et al	USA	47	under 18, lower age bound not reported	psychiatric patients	topiramate or zonisamide	Another treatment	NA	reduction in body mass index	retrospective cohort	Electronic health records
Shehab et al	USA	Not applicable	under 5 through 17, lower age bound not reported	Emergency Department patients with adverse drug events	Hematologic, systemic antimicrobial, hormone-modifying, central nervous system, cardiovascular, oncological and immunologic, musculoskeletal, respiratory, gastrointestinal agents and other drug classes.	Another treatment	Emergency department visits for adverse drug events	NA	case-control	Manual record review and/or primary data collection
Shein et al	USA	25	2-14	Traumatic brain injury	fentanyl, 3% sodium chloride hypertonic saline, mannitol or pentobarbital	Another treatment	NA	reduction in intracranial pressure	prospective cohort	Manual record review and/or primary data collection

Author	Country(ies) where study was conducted	Sample size in studies where study population is under 18	Age range	Disease or condition defining the patient population	Medication(s) in exposure or treatment group	Comparator/ control group	Primary safety endpoint	Primary effectiveness endpoint	Study design	Data collection
Sheridan et al	US	Not applicable	not reported	migraine headache	dopamine antagonists (prochlorperazine, metoclopramide, and promethazine), dihydroergotamine, parental valproate, magnesium, diphenhydramine, triptans, or nonsteroidal anti-inflammatory drugs or opioid medications	Another treatment	NA	hospital length of stay	retrospective cohort	Electronic health records
Shin et al	South Korea	1224	under 18, lower age bound not reported	Attention deficit hyperactivity disorder	methylphenidate	Self-controlled	Cardiovascular events	NA	self-controlled	Administrative claims
Sirois et al	US, Puerto Rico	524	3-16	Human immune-deficiency virus	methylphenidate or amphetamine salts	Unexposed or untreated	NA	measures of cognition, behavior, and quality of life	prospective cohort	Manual record review and/or primary data collection
Suruki et al	USA	734114	0-17	Asthma	asthma medication (e.g. short-acting beta agonist, inhaled corticosteroid [ICS], ICS plus long-acting beta agonist, leukotriene receptor antagonist or omalizumab)	Different dose	NA	asthma exacerbations	retrospective cohort	Administrative claims
Tappeiner et al	Germany	Not applicable	not reported	Juvenile idiopathic arthritis	Disease-modifying antirheumatic drugs	Another treatment	NA	Uveitis (prevention)	prospective cohort	Registry

Author	Country(ies) where study was conducted	Sample size in studies where study population is under 18	Age range	Disease or condition defining the patient population	Medication(s) in exposure or treatment group	Comparator/ control group	Primary safety endpoint	Primary effectiveness endpoint	Study design	Data collection
Tey et al	Taiwan	104	Very low birth weight infants	Very low birth weight infants	Aminophylline	Unexposed or untreated	Neuro-developmental impairment	NA	retrospective cohort	Manual record review and/or primary data collection
van der Schans et al	Netherlands	7994	12-13	psychiatric patients	antipsychotics	Unexposed or untreated	NA	school performance	retrospective cohort	Administrative claims
Verazza et al	Italy	1038	1-15	Juvenile idiopathic arthritis	etanercept	Unexposed or untreated	No primary endpoint specified	Juvenile idiopathic arthritis progression	retrospective cohort	Manual record review and/or primary data collection
Wang et al	Australia	Not applicable	3-18	pulmonary embolism	oral contraceptives	Unexposed or untreated	Pulmonary embolism	NA	case-control	Manual record review and/or primary data collection
Webb et al	UK	104	1-15	nephrotic syndrome	cyclophospha-mide	Another treatment	No primary endpoint specified	relapse of nephrotic syndrome	retrospective cohort	Manual record review and/or primary data collection

eTable S2. GRACE assessment scoring items D1-D6

Author	D1. Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data source(s)?	D2. Were the primary outcomes adequately recorded for the study purpose?	D3. Was the primary clinical outcome(s) measured objectively rather than subject to clinical judgment?	D4. Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	D5. Was the primary outcome(s) measured or identified in an equivalent manner between the treatment/intervention group and the comparison group?	D6. Were important covariates that may be known confounders or effect modifiers available and recorded?
Barger-Kamate et al	0	1	1	1	1	0
Barnard-Brak et al	0	1	1	1	1	0
Barth et al	1	1	1	1	1	1
Batton et al	1	1	1	1	1	1
Berkenwald et al	1	1	1	1	1	1
Brown et al	1	1	1	1	1	1
Duerden et al	1	1	1	1	1	0
Gracious et al	1	1	1	1	1	1
Horton et al	1	1	1	1	1	1
Knupp et al	1	1	1	1	1	0
Kostik et al	1	1	1	1	1	0
Li et al	0	1	1	1	1	0
Pandya et al	1	1	1	1	1	0
Schwarz et al	1	0	0	0	0	1
Scott et al	1	1	1	1	1	1
Sdona et al	0	1	1	1	1	1
Shapiro et al	1	1	1	1	1	1
Shehab et al	0	1	0	1	1	1
Shein et al	1	1	1	1	1	1
Sheridan et al	0	1	1	1	1	0
Shin et al	1	1	1	1	1	1
Sirois et al	0	1	1	1	1	0
Suruki et al	1	1	1	1	1	0
Tappeiner et al	0	0	1	1	1	1
Tey et al	1	1	1	1	1	1
van der Schans et al	1	1	1	1	1	1
Verazza et al	1	1	1	1	1	0
Wang et al	1	1	1	1	1	1
Webb et al	1	1	1	1	1	1
Total scored as positive	21	27	27	28	28	18
Percentage of total	72	93	93	97	97	62

eTable S2 cont'd GRACE assessment scoring items M1-M5 and total scores for each article

Author	M1. Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?	M2. If 1 or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparison groups?	M3. Were important confounding and effect-modifying variables taken into account in the design and/or analysis?	M4. Is the classification of exposed and unexposed person-time free of "immortal time bias,"?	M5. Were any meaningful analyses conducted to test key assumptions on which primary results are based?	Total score for study
Barger-Kamate et al	1	1	0	1	0	7
Barnard-Brak et al	0	1	0	1	0	6
Barth et al	0	1	0	0	0	7
Batton et al	0	1	1	0	0	8
Berkenwald et al	0	1	1	0	0	8
Brown et al	0	1	1	0	1	9
Duerden et al	0	1	1	0	0	7
Gracious et al	1	1	1	0	0	9
Horton et al	1	1	1	0	1	10
Knupp et al	0	1	1	0	0	7
Kostik et al	0	1	0	0	0	6
Li et al	1	0	1	1	0	7
Pandya et al	0	0	0	1	0	6
Schwarz et al	0	1	0	1	0	4
Scott et al	0	1	1	1	1	10
Sdona et al	1	1	1	1	1	10
Shapiro et al	1	0	1	1	1	10
Shehab et al	0	0	0	0	0	4
Shein et al	1	1	1	1	1	11
Sheridan et al	0	1	0	0	0	5
Shin et al	0	1	1	1	1	10
Sirois et al	1	1	0	0	0	6
Suruki et al	0	0	0	1	1	7
Tappeiner et al	0	1	1	0	0	6
Tey et al	1	1	1	1	1	11
van der Schans et al	0	1	1	1	1	10
Verazza et al	1	1	0	1	1	9
Wang et al	0	1	1	1	0	9
Webb et al	1	1	0	0	0	8
Total scored as positive	11	24	17	15	11	
Percentage of total	38	83	59	52	38	