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The impact of non-medical switching among ambulatory patients: an updated systematic literature review

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ABSTRACT

Background: Non-medical switching (NMS) is defined as switching to a clinically similar but chemically distinct medication for reasons apart from lack of effectiveness, tolerability or adherence.
Objective: To update a prior systematic review evaluating the impact of NMS on outcomes.
Data sources: An updated search through 10/1/2018 in Medline and Web of Science was performed.
Study selection: We included studies evaluating ≥25 patients and measuring the impact of NMS of drugs on ≥1 endpoint.
Data extraction: The direction of association between NMS and endpoints was classified as negative, positive or neutral.
Data synthesis: Thirty-eight studies contributed 154 endpoints. The direction of association was negative (n = 48; 31.2%) or neutral (n = 91; 59.1%) more often than it was positive (n = 15; 9.7%). Stratified by endpoint type, NMS was associated with a negative impact on clinical, economic, healthcare utilization and medication-taking behavior in 26.9%,41.7%,30.3% and 75.0% of cases; with a positive effect seen in 3.0% (resource utilization) to 14.0% (clinical) of endpoints. Of the 92 endpoints from studies performed by the entity dictating the NMS, 88.0%were neutral or positive; whereas, only 40.3%of endpoints from studies conducted separately from the interested entity were neutral or positive.
Conclusions: NMS was commonly associated with negative or neutral endpoints and was seldom associated with positive ones.

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KEYWORDS
Managed care; non-medical switch; outcome assessment; therapeutic interchange

Introduction

Non-medical switching is typically defined as a change in a patient's medication to a clinically similar but chemically distinct (i.e., not a bioequivalent generic) medication for reasons apart from lack of clinical effectiveness, tolerability or adherence [1,2]. An underlying cause of non-medical switching involves formulary changes aimed at decreasing the acquisition cost of prescription medications. While such practices will likely result in decreased costs of procuring the target medication, non-medical switching has been associated with unintended consequences [3]. A prior systematic review of 29 studies (published prior to November 2015) evaluating ambulatory patients suggested non-medical switching was frequently associated with a negative impact on clinical and economic endpoints, overall resource utilization (not just target medication acquisition costs) and patient adherence or persistence to their prescribed medication regimens [3].

Since the publication of this prior systematic review, a great deal of attention has been paid to the consequences of non-medical switching by medical and patient advocate organizations and state legislatures [4–7] and new studies/data have been generated and published [8–18]. Both the Cochrane Handbook for Systematic Reviews of Interventions [19] and the methods guide for the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center program [20] remark on the importance of updating of a systematic review as new evidence becomes available. Therefore, we performed an update of the prior systematic review with the aim of further evaluating current knowledge of the impact of non-medical switching on clinical and economic endpoints, resource utilization and medication-taking behaviors.

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Materials and methods

Preparation of this report was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. The goal of this guideline is to facilitate the transparent reporting of systematic reviews and meta-analyses to assess the benefits and harms of a health-care intervention.

Search strategy

We performed an updated systematic literature search from November 2015 (end date of prior systematic literature search) through 1 October 2018 in Medline and Web of Science (WoS) using the same search strategy as the prior review (Table 1). WoS was selected as a second literature source to maximize capture of abstracts from major medical and managed care meetings. The search was limited to human studies in the English language and excluded case studies, editorials and review articles. Bibliographical database searches were augmented by manual searches of the reference sections of relevant studies ('backward citation tracking') and a review of the first 500 results of a Google Scholar search.

Study selection

Two investigators screened citations and assessed eligible studies for inclusion in duplicate with disagreement reconciled through discussion and consensus. Studies were included in this review if they were real-world studies performed in the USA (US), included ≥25 patients and evaluated the impact of non-medical switching of prescription drugs on at least one endpoint of interest. For the purposes of this review, non-medical switching was defined as switching to a chemically distinct but clinically similar medication for reasons other than lack of clinical efficacy or response, adverse effects or poor adherence. Outcomes of interest for this review included clinical (i.e., any measure of patient health including patient satisfaction), economic (i.e., medical or treatment costs, excluding index drug costs), resource utilization (i.e., office or emergency room visits or hospitalizations) and medication-taking behavior (i.e., adherence, persistence or discontinuation). Studies evaluating the impact of simple brand to generic substitution, changes in dosage form or route of administration or evaluating temporary (i.e., in-hospital) non-medical switches were excluded.

Table 1. MEDLINE search strategy.

'medication conversion' OR 'drug conversion' OR 'non-medical switch$' OR 'nonmedical switch$' OR 'non-consented switch$' OR 'therapeutic switch$' OR 'therapeutic interchange' OR 'therapeutic substitution' OR 'drug substitution' OR 'nonmedical switcher$' OR 'generic switch$' OR 'switcher$' OR 'non-medical reason') AND ('Adherence' OR 'compliance' OR 'persistence' OR 'medication discontinuation' OR 'drug utilization' OR 'quality of life' OR 'patient satisfaction' OR 'drug cost$' OR 'medication cost$' OR 'drug spending' OR 'medication spending' OR 'drug acquisition cost$' OR 'medication acquisition cost $' OR 'healthcare cost$' OR 'health care cost$' OR 'cost saving$' OR 'medical resource$' OR 'healthcare services' OR 'health care services' OR 'resource utilization' OR 'resource use' OR 'emergency room visit$' OR 'emergency department visit$' OR 'ER visit$' OR 'ED visit$' OR 'economic consequence$' OR 'clinical impact' OR 'disease activity' OR 'effectiveness' OR 'side effect$' OR 'adverse effect$' OR 'outcome$' OR 'total cost$' OR 'pharmacy cost$')

Data abstraction

Two investigators, through use of a standardized tool, independently abstracted all data with disagreements resolved by discussion. The following data were sought from each study: first author's last name, year of publication; medication(s) switched; primary disease state; data source; duration of follow-up; data required for validity assessment (including whether the study was performed by the entity responsible for/dictating the non-medical switch; Appendix 1); funding source; whether disease stability prior to the switch was adequately demonstrated; endpoint type (clinical, economic, health-care utilization, medication-taking behavior); and direction and statistical significance of association between non-medical switching and each reported endpoint(s).

Validity assessment

The internal validity of the included studies was assessed using an adapted version of the Newcastle–Ottawa Scale (NOS) (Appendix 1) [22]. A total of eight items within four domains (selection of study group, comparability of study group, ascertainment of exposure and 'other') were evaluated. Under the domain 'other', we assessed whether studies were performed separately from the entity responsible for dictating the non-medical switch. If a study satisfactorily met a criterion, a star (*) was assigned for that item; otherwise a minus sign (-) was noted. Each study was assessed by two investigators independently, with disagreements resolved through discussion and consensus.

Data synthesis

The direction of the association between non-medical switching and each individual endpoint identified within included studies was classified as negative, positive or neutral. An association was deemed 'negative' if the non-medical switch reflected a worsening of the endpoint and was statistically significant. For example, endpoints reflecting decreased adherence, worsened clinical outcomes, increased health-care utilization or increased costs were deemed negative. 'Positive' associations were those in

which the endpoint improved in a statistically significant manner. For example, endpoints reflecting increased adherence, improved clinical outcomes, decreased healthcare utilization or decreased costs were deemed positive. If no statistically significant relationship was observed between the switch and the endpoint, the direction of association was deemed 'neutral'. In all cases, the p-value used to conclude statistical significance was based on each study's defined p-value. Statistical significance was not reported for three usable endpoints from 2 studies; thus, we independently analyzed the data to estimate a p-value [12,23]. When studies reported overlapping endpoints (e.g., any hospitalization versus disease-specific hospitalization), the most disease-specific endpoint was included. If a datapoint was reported by a study in both a continuous and dichotomous way (e.g., hemoglobin A1c value versus attainment of goal hemoglobin A1c [11]) the continuous endpoint was preferentially used as it provides a higher level of information. We did not evaluate economic endpoints that included the change in index (for non-medical switching) medication costs in the overall analysis, but did report these costs separately.

The overall frequency in which non-medical switching was associated with a negative, neutral or positive impact on all endpoints was reported as percentages. As with the prior systematic review, each included study was classified into one of the two 'non-medical switching' categories based on whether disease stability prior to the switch was demonstrated. Category (A) consisted of studies in which patients were demonstrated to have stable or well-controlled disease; whereas, Category (B) studies did not attempt to document this. The definition of stable or well-controlled disease varied across included studies but generally required patients to meet objective, disease-specific endpoints (e.g., laboratory values or vital signs) or not requiring supplemental resource utilization (e.g., emergency room visits or hospitalizations) within a defined period prior to the non-medical switch. The frequencies of each type of endpoint were stratified by the direction of association, non-medical switch category (A or B) and endpoint type. Additional stratified analyses were performed to determine if there was a time trend in the number and results of non-medical switching studies (2015–2018, 2010–2014, 2005–2009, 2000–2004), if the results (frequency in which endpoints were negative, neutral or positive) varied by duration of study follow-up (<6 months versus ≥6 months) or between studies performed by the entity responsible for/dictating the non-medical switch (to assess the potential for reporting biases). For all stratified analyses, the direction of the association between non-medical switching and each individual endpoint was again classified negative, positive or neutral via the definitions utilized in the summary of the overall results.

Results

Study characteristics

The initial search strategy yielded 3,177 citations and an additional 14 citations were manually identified (Figure 1). After screening and full-text assessment, 38 studies (11 studies added based on the updated search) with a total of 260,256 patients (median: 591; range: 31–102,076) and a median follow-up of 6 months (range: 0.5 to 18 months) were included in our review (Table 2) [8–18,23–49]. A total of 26 studies (68.4%) were published between 2000 and 2014, while 12 (31.6%) were published between 2015 and 2018. A majority of studies (n = 23; 60.5%) assessed the impact of non-medical switching in cardio-metabolic disease including hypertension, hyperlipidemia or diabetes, followed by immune-mediated conditions (n = 5; 13.2%), acid suppression (n = 3; 7.9%), psychiatric disorders (n = 2; 5.3%) and other miscellaneous other conditions (n = 5; 13.2%). The largest proportion of studies acquired data through chart review (n = 16; 42.1%), followed by claims (n = 9; 23.7%), claims with integrated electronic health records (n = 7; 18.4%) and other methods (n = 6; 15.8%). Twenty (52.6%) studies were externally funded. According to non-medical switch categories A (patients with stable/well-controlled disease) and B (patients without documented stable/well-controlled disease), there were 11 (28.9%) and 27 (71.1%) studies, respectively. A total of 25 (65.8%) studies were performed by the entity responsible for/dictating the non-medical switch.

Validity assessment results

Upon validity assessment using the NOS, only 4 of the 38 studies were given a minus sign in >1 evaluated item, suggesting a lower risk of bias in most included studies (Appendix 2). One study in category B relied on patient self-report for the ascertainment of the non-medical switch and was not awarded a star for this item [12]. Three studies (one in category A and two in category B) were unmatched and were not given a star for comparability of study population. Three studies (all in category B) did not meet criteria for low risk of bias within one of the endpoint domains because they utilized either a subjective outcome and/or the duration or completeness or follow-up were inadequate. Finally, 25 studies were not awarded a star because they were performed by the entity dictating the non-medical switch.

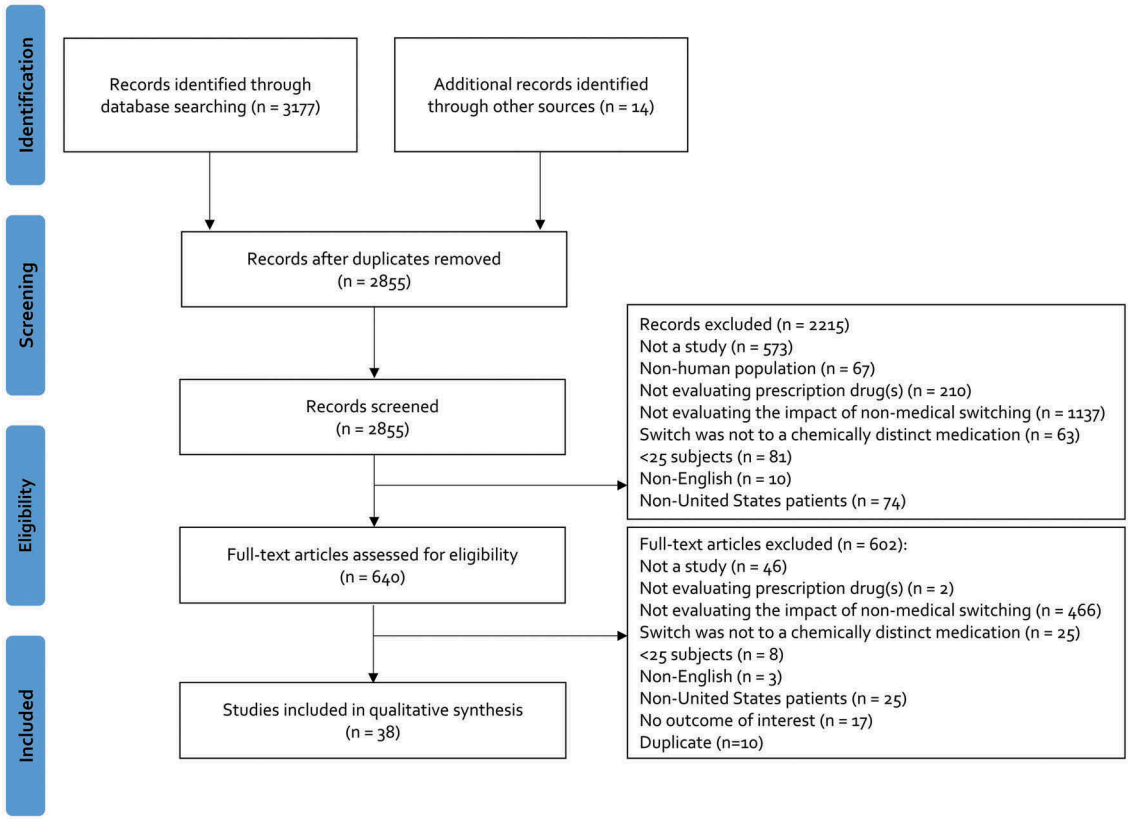

Figure 1. Flow Diagram of Study Selection Process*.

*"Not a study" refers to a citation that was excluded because it was not a primary literature source (e.g., review articles, editorials)

Endpoint level results

The 38 included studies reported 154 eligible endpoints (64 added based on updated search). The most frequent outcome type was clinical (n = 93; 60.4%), followed by resource utilization (n = 33; 21.4%), economic (n = 24; 15.6%) and medication-taking behavior (n = 4; 2.6%) (Table 3). Nearly 40% (n = 65) of outcomes were from studies published between 2015 and 2018. Forty-nine (31.8%) of the endpoints came from category A studies (i.e., those requiring patients to have stable/well-controlled disease). Two-thirds of endpoints were from studies that followed patients for ≥6 months (n = 97; 63.0%) and more than half were from a study performed by the entity dictating the non-medical switch (n = 92; 59.7%). Qualitatively, the direction of association was negative (n = 48; 31.2%) or neutral (n = 91; 59.1%) more often than it was positive (n = 15; 9.7%).

When stratified by outcome type, non-medical switching was associated with a negative impact on clinical, economic, health-care utilization and medication-taking behavior outcomes in 26.9%, 41.7%, 30.3% and 75.0% of cases, respectively; and a positive effect was seen in only 3.0% (resource utilization) to 14.0% (clinical) of outcomes (Figure 2-I). Only seven studies reported index drug costs and the effects were negative, neutral and positive in two, one and four studies, respectively.

When analysis was restricted to category A studies (patients with stable/well-controlled disease), 28 (57.1%) and 21 (42.9%) had a negative and neutral direction of association (Figure 2-II). Non-medical switching was not positively associated with any outcome in category A studies. Most clinical outcomes had a negative direction of association (n = 13; 72.2%). All medication-taking behavior outcomes (n = 2; 100%), half (n = 9) of all resource utilization outcomes and 36.4% (n = 4) of economic outcomes were negative. Out of a total of 105 outcomes in category B (patients without documented stable/well-controlled disease), the direction of association was negative for 20 (19.0%) outcomes, neutral for 70 (66.7%) outcomes, and positive for 15 (14.3%) outcomes (Figure 2-III). The majority of clinical and resource utilization outcomes were neutral (n = 50; 66.7% and n = 13; 86.7%, respectively). Half of mediation taking behavior outcomes (n = 1) and 46.2% (n = 6) of economic outcomes were negative.

Table 2. Characteristics of included studies.

Reference	Drug(s) Switched; Disease(s)	Data Source; Comparison Type	Funding Source	Follow-up Period	Stable/well-controlled disease	Outcome Type	Outcome	Direction of Association
Blonde [11] N = 1,336	Canagliflozin to different anti-glycemic agent; DM	IQVIA RWD and longitudinal prescription database; matched	Janssen Research and Development	4 months	No	Clinical	Unique anti-glycemic products used	Negative
							Anti-hypertensive medication use	Negative
							Dyslipidemia medication use	Negative
						Economic	Total diabetes-related medical costs	Negative
							Diabetes-related hospitalization costs	Neutral
							Diabetes-related ED visit costs	Neutral
							Diabetes-related outpatient visit costs	Neutral
							Diabetes-related laboratory and pathology costs	Neutral
							Diabetes-related costs for other services	Neutral
							Non-diabetes related outpatient pharmacy costs	Positive
						Resource utilization	Diabetes-related pharmacy fills	Negative
						Medication Taking Behavior	Discontinuation or switch	Negative
Flores [12] N = 379	Anti-glycemic agent to different anti-glycemic agent; DM	Internet-based patient survey; Pre/post	Janssen Scientific Affairs	NR	No	Clinical	Treatment satisfaction	Negative
Gibofsky [8] N = 4,962	Anti-TNF to different anti-TNF; RA, PS, PsA, AS, CD, UC	Humedica EHR data; Matched	Abbvie	12 months	Yes	Clinical	Any physician documented adverse clinical consequence	Negative
							Side effect	Negative
							Diminished efficacy	Negative
							Subsequent medication change	Negative
							Subsequent medication changes related to adverse consequence	Negative
						Resource Utilization	Inpatient visit	Neutral
							ER visit	Neutral
							Ambulatory visit	Negative
Naville-Cook [13] N = 1,520	Rosuvastatin to atorvastatin; HLD	VA; Pre/post	None	12 months	No	Clinical	LDL	Neutral
							ALT	Neutral
							AST	Neutral
							CPK	Neutral
							Alkaline phosphatase	Negative
							MI	Neutral
							Stroke	Neutral
							Stent placement	Neutral
Rosenblatt [9] N = 1,155	First line ART to alternative ART; HIV	Optum Research Database and Impact National Benchmark Database; Matched	Bristol-Myers Squibb	18 months	Yes	Clinical	Virologic failure	Neutral
							Next ART Change	Negative
						Economic	Inpatient costs	Neutral
							ER costs	Neutral
							Ambulatory costs	Neutral
							Other medical costs	Neutral
						Resource Utilization	Inpatient visits	Neutral
							Length of inpatient visit in days	Neutral
							ER visits	Neutral
							Ambulatory visits	Neutral
Wolf [10] N = 754	Anti-TNF to different anti-TNF; CD, UC, RA, AS, PS, PsA	Gastroenterologist, rheumatologist, and dermatologist chart review at multiple sites; Matched	Abbvie	12 months	Yes	Clinical	Disease flares	Negative
							Well-controlled disease	Negative
						Resource Utilization	Inpatient visits	Negative
							ER visits	Negative
							Outpatient visits	Negative

(*Continued*)

Table 2. (Continued).

Reference	Drug(s) Switched; Disease(s)	Data Source; Comparison Type	Funding Source	Follow-up Period	Stable/well-controlled disease	Outcome Type	Outcome	Direction of Association
Boktor [14] N = 60	Infliximab or Adalimumab to Certolizumab; CD	Louisiana State University Health Sciences Center EHR data; Pre/post	None	12 months	No	Clinical	ESR	Neutral
							CRP	Neutral
							Hemoglobin	Neutral
							Albumin	Neutral
							WBC	Neutral
							CDAI	Neutral
Yip [15] N = 521	Fluticasone/salmeterol to mometasone/ formoterol; COPD	Kaiser Permanente; Pre/post	None	6 months	No	Clinical	COPD exacerbation	Positive
							Required modification in therapy	Neutral
						Resource Utilization	Inpatient visits for COPD exacerbation	Neutral
							ED or urgent care visits for COPD exacerbation	Neutral
							Outpatient encounter for COPD exacerbation	Neutral
							ICU admission for COPD exacerbation	Neutral
Andreoli [16] N = 77[a]	Ranibizumab to bevacizumab; Neovascular AMD	Harvard Vanguard Medical Associates EHR data; Pre/post	NR	10 months	No	Clinical	Mean Vision	Neutral
							Injections per year	Neutral
							OCT CSF thickness	Neutral
Asias [17] N = 133	Insulin glargine to insulin detemir; DM	VA; Pre/post	None	3-9 months	No	Clinical	Hemoglobin A1C	Negative
							Long acting insulin dose	Negative
							Weight	Positive
							BMI	Positive
Liu [24] N = 3,678	Adalimumab to different biologic (certolizumab, golimumab, etanercept, or ustekinumab); RA, PS, PsA, AS, CD	OptumInsight Database; Unmatched	Abbvie	6 months	Yes	Economic	All-cause medical costs	Negative
Low [18] N = 1,280	Atorvastatin to simvastatin; HLD	Massachusetts General Physicians Organization EHR data; Unmatched	None	12 months	No	Clinical	LDL	Neutral
Bryant [39] N = 31	Insulin glargine to insulin detemir; DM	Iowa academic medical center EHR data; Pre/post	NR	12 months	No	Clinical	Goal hemoglobin A1C	Neutral
							Weight gain	Neutral
							Hypoglycemia	Neutral
Saseen [25] N = 3,412	Olmesartan to different ARB; HTN	GE Healthcare's Centricity EMR Database; Adjusted	Daiichi Sankyo	1-13 months	Yes	Clinical	SBP <140 mmHg	Negative
							DBP <90 mmHg	Negative
Alemayehu [40] N = 75,560	Esomeprazole to different PPI; Acid suppression	Ingenix LabRx Database; Unmatched	AstraZeneca	6 months	No	Economic	GI-related medical service costs	Negative
							Non-PPI prescription costs	Negative
Kamal [34] N = 258	ARB to different ARB; HTN	GE Healthcare's Centricity EMR Database; Matched	Novartis Pharmaceuticals	6 months	Yes	Clinical	SBP	Negative
							DBP	Neutral
							Addition of other anti-HTN medications	Negative
						Resource Utilization	Office visits	Neutral
Signorvitch 2012 N = 6,270	Adalimumab to different DMARD; RA	MarketScan; Adjusted	Abbot Laboratories	6 months	Yes	Resource Utilization	ER visits	Negative
							RA outpatient visits	Negative
						Medication Taking Behavior	Discontinuation	Negative
West [36] N = 661	Psychiatric medications; Psychiatric conditions	Psychiatrist chart review at multiple sites; Matched	APF[b] and AHRQ	12 months	Yes	Clinical	Adverse events (in patients switched to a medication within the same class)	Neutral
							Adverse events (in patients switched to an interchangeable medication in a different class)	Negative
Wu [37] N = 8,898	Brand SSRI to different generic SSRI; MDD	Ingenix Impact Database; Matched	Forest Research Institute	6 months	Yes	Economic	MDD-related medical cost	Negative
						Resource Utilization	MDD-related hospitalization	Negative
							MDD-related ER visits	Neutral

(*Continued*)

Table 2. (Continued).

Reference	Drug(s) Switched; Disease(s)	Data Source; Comparison Type	Funding Source	Follow-up Period	Stable/well-controlled disease	Outcome Type	Outcome	Direction of Association
Signorvitch 2010 N = 102,076	Valsartan to different ARB; HTN	MarketScan; Matched	Novartis Pharmaceuticals	6 months	Yes	Economic	Total medical costs excluding ARB cost	Negative
							HTN-related medical services	
							Inpatient costs	Negative
							ER costs	Neutral
							Outpatient costs	Neutral
							Non-ARB hypertensive drug cost	Neutral
						Resource Utilization	HTN-related medical services	
							Inpatient days	Negative
							ER visits	Neutral
							Outpatient visits	Negative
						Medication Taking Behavior	Discontinuation	Negative
Miller [41] N = 117	Atorvastatin to simvastatin, rosuvatatin or ezetimibe-simvastatin; HLD	University of Colorado Healthcare System EHR data; Pre/post	NR	1-13 months	No	Clinical	LDL	
							Usual care	Negative
							Conversion by pharmacist	Neutral
							HDL	
							Usual care	Neutral
							Conversion by pharmacist	Neutral
							Triglycerides	
							Usual care	Neutral
							Conversion by pharmacist	Neutral
Gates [27] N = 364	Fosinopril to benazepril; HTN	VA; Pre/post	NR	4 months	No	Clinical	SBP	Neutral
							DBP	Neutral
							Estimated GFR	Neutral
							Serum potassium	Neutral
Meissner [42] N = 3,636	Atorvastatin to different statins (simvastatin, lovastatin, pravastatin, or fluvastatin); HLD	Segment of multistate Medicaid MCO claims database; Pre/post	None	12 months	No	Economic	Statin therapy medical management costs	Neutral
Billlups 2005 N = 5,046	Simvastatin to lovastatin; HLD	Kaiser Permanente; Pre/post	None	≥1.5 months	No	Clinical	LDL	Positive
							ALT	Neutral
						Medication Taking Behavior	Adherence	Neutral
Cheetham [23] N = 33,318	Simvastatin to lovastatin; HLD	Kaiser Permanente; Pre/post	NR	3-15 months	No	Clinical	LDL	Positive
							HDL	Positive
							Triglycerides	Positive
							Marked ALT	Neutral
							Marked CK	Neutral
Tran [43] N = 32	Celecoxib or rofecoxib to valdecoxib; OA, RA, pain	VA patient interviews; Pre/post	NR	0.5 months	No	Clinical	Pain	Neutral
Manzo [29] N = 68	Amlodipine to felodipine; HTN	VA; Pre/post	AstraZeneca	6 months	No	Clinical	SBP	Neutral
							DBP	Neutral
							Heart rate	Positive
Graham [30] N = 72	Losartan or valsartan to irbesartan; HTN	VA; Pre/post	Bristol-Myers Squibb	2 months	No	Clinical	SBP	Neutral
							DBP	Neutral
							Heart rate	Neutral
							Adverse drug reactions	Neutral
Taylor [31] N = 942	Atorvastatin, fluvastatin, pravastatin, low-dose simvastatin (<80 mg/day) and cerivastatin (<0.4 mg/day) to cerivastatin (0.4 or 0.8 mg/day) or simvastatin (80 mg/day); HLD	Chart review at Walter Reed Army Medical Center; Pre/post	Bayer Pharmaceutical Corporation	1.5 months	No	Clinical	LDL	Positive
							HDL	Positive

(*Continued*)

Table 2. (Continued).

Reference	Drug(s) Switched; Disease(s)	Data Source; Comparison Type	Funding Source	Follow-up Period	Stable/well-controlled disease	Outcome Type	Outcome	Direction of Association
Andrade [44] N = 2,235	Conjugated to esterified estrogen or different HRT medication; HRT	Fallon Community Health Plan HMO Claims data; Pre/post	Solvay Pharmaceuticals	6 months	No	Resource Utilization	Ambulatory visits related to HRT	
							Switched to different HRT	Neutral
							Switched to esterified estrogen	Neutral
Clay [45] N = 113	Amlodipine to felodipine; HTN/angina	Chart review at Naval Health Clinic Charleston; Pre/post	NR	12 months	No	Clinical	BP <140/90 mmHg	Neutral
							Use of other anti-HTN medications	Neutral
Fugit [26] N = 96	Simvastatin to lovastatin; HLD	VA; Pre/post	NR	3 months	Yes	Clinical	Lipid tests	Neutral
							Liver function tests	Neutral
Good [32] N = 704	Nizatidine to cimetidine; duodenal and gastric ulcer disease, GERD	VA; Pre/post	NR	6 months	No	Resource Utilization	Clinic visits	Neutral
							GI-related admissions	Neutral
							Abdominal CT	Neutral
							Barium studies	Positive
							Endoscopic studies	Neutral
Mamdani [46] N = 101	Nifedipine extended-release to amlodipine or felodipine; HTN	VA; Pre/post	Astra-Merck	9 months	No	Clinical	SBP	Positive
							DBP	Positive
							Drug utilization (prescriptions for any medication/patient)	Negative
						Economic	Cardiovascular drug cost[c]	Negative
							Non-cardiovascular drug cost	Negative
						Resource Utilization	Clinic visits	Neutral
							Emergency room visits	Neutral
							Hospitalizations	Neutral
Nelson [47] N = 105	Omeprazole to lansoprazole; heartburn, GERD	Interviews of patients identified in Unity Prescription Database; Pre/post	TAP Pharmaceuticals	1 month	No	Clinical	Heartburn symptom severity	Negative
							Overall patient satisfaction	Negative
Oatis [33] N = 142	Amlodipine to felodipine extended-release; HTN/angina	Chart review at Barksdale Air Force Base Pharmacy; Pre/post	NR	6-9 months	No	Clinical	Concomitant cardiovascular medications	Negative
						Economic	Concomitant cardiovascular drug cost	Negative
Parra [49] N = 100	Amlodipine to different CCB (felodipine; SR nifedipine, SR verapamil, SR diltiazem); HTN	VA; Pre/post	AstraZeneca	5 months	No	Clinical	SBP	Neutral
							DBP	Positive
							Pulse	Neutral
Walters [49] N = 44	Amlodipine to felodipine extended-release; HTN	VA; Pre/post	NR	2-6 months	No	Clinical	SBP	Neutral
							DBP	Neutral
							Heart rate	Neutral
							PR interval	Neutral
							QRS interval	Neutral
							QTc interval	Neutral

[a]Represents number of eyes treated.
[b]AFP received financial support from a consortium of industry supporters.
[c]Excluding prescriptions for the index therapy.
AHRQ = Agency for Healthcare Research and Quality; ALT = alanine aminotransferase; AMD = age-related macular degeneration; APF = American Psychiatric Foundation; ARB = angiotensin receptor blocker; ART = antiretroviral therapy; AS = ankylosing spondylitis; AST = aspartate transaminase; BMI = body mass index; BP = blood pressure; CCB = calcium channel blocker; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CK = creatine kinase; COPD = chronic obstructive pulmonary disease; CPK = creatine phosphokinase; CSF = central subfield thickness; CT = computerized tomography; DBP = diastolic blood pressure; DM = diabetes mellitus; DMARD = disease-modifying antirheumatic drug; EHR = electronic health record; EMR = electronic medical record; ER = emergency room; ESR = erythrocyte sedimentation rate; GE = General Electric; GERD = gastroesophageal reflux disease; GFR = glomerular filtration rate; GI = gastrointestinal; HIV = human immunodeficiency virus; HDL = high density lipoprotein; HLD = hyperlipidemia; HRT = hormone replacement therapy; HTN = hypertension; ICU = intensive care unit; LDL = low-density lipoprotein; MAP = mean arterial pressure; MCO = managed care organization; MI = myocardial infarction; MDD = major depressive disorder; N = sample size; NMS = non-medical switch; NR = not reported; OA = osteoarthritis; OCT = optical coherence tomography; PPI = Proton Pump Inhibitor; PS = psoriasis; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RWD = real-world data; SBP = systolic blood pressure; SR = sustained release; SSRI = selective serotonin reuptake inhibitor; TNF = tumor necrosis factor; UC = ulcerative colitis; VA = Veterans Affairs; WBC = white blood cell.

Table 3. Overall sub-classification of outcomes.

Outcome sub-classification	n (%)
Non-medical switch category	
Category A (stable/well-controlled disease)	49 (31.8)
Category B (no requirement for stable/well-controlled disease)	105 (68.2)
Type	
Clinical	93 (60.4)
Economic	24 (15.6)
Resource utilization	33 (21.4)
Medication taking behavior	4 (2.6)
Disease State	
Cardio-metabolic	95 (61.7)
Immune-mediated disorders	23 (14.9)
Human immunodeficiency virus	10 (6.5)
Acid suppression	9 (5.8)
Other[a]	17 (11.0)
Publication Year	
2015-2018	65 (42.2)
2010-2014	28 (18.2)
2005-2009	19 (12.3)
2000-2004	42 (27.3)
Follow-up[b]	
≥6 months	97 (63.0)
<6 months	56 (36.4)
Entity conducting study	
Performed by entity dictating non-medical switch	92 (59.7)
Not performed by entity dictating non-medical switch	62 (40.3)

[a]Other included chronic obstructive pulmonary disease (n = 6), psychiatric (n = 5), age-related macular degeneration (n = 3), hormone replacement therapy (n = 2), pain (n = 1).
[b] Duration of follow-up was not reported for one outcome.

A greater proportion of endpoints from studies published between 2015 and 2018 were negative when compared to outcomes from studies published before 2015 (35.4% versus 28.1%; Figure 3-I). Endpoints from studies with a duration of follow-up ≥6 months were also more frequently negative (35.1% versus 23.2% in studies with <6 months of follow up; Figure 3-II). Nearly 90% of endpoints from studies performed by the entity dictating the non-medical switch were neutral or positive; whereas, only 40.3% of endpoints from studies not conducted by the entity mandating the switch were neutral or positive (Figure 3-III).

Discussion

In this updated systematic review, non-medical switching continued to be frequently associated with negative outcomes. Less than 10% of endpoints had a positive direction of association. Among the subset of studies including patients with stable/well-controlled disease, non-medical switching was most frequently associated with negative clinical endpoints, and non-medical switching was not positively associated with any endpoint in this subset.

Most endpoints in the present systematic review were from studies performed by the same entity dictating/requiring the non-medical switch. Of these outcomes, ~90% were neutral or positive, while the majority of endpoints in studies conducted separately from the entity dictating the non-medical switch were negative. This suggests the possibility of reporting biases, as studies showing an intervention are not beneficial are less likely to be published. Future studies evaluating non-medical switching should be performed by researchers unrelated to the entities mandating the switch to remove such potential biases.

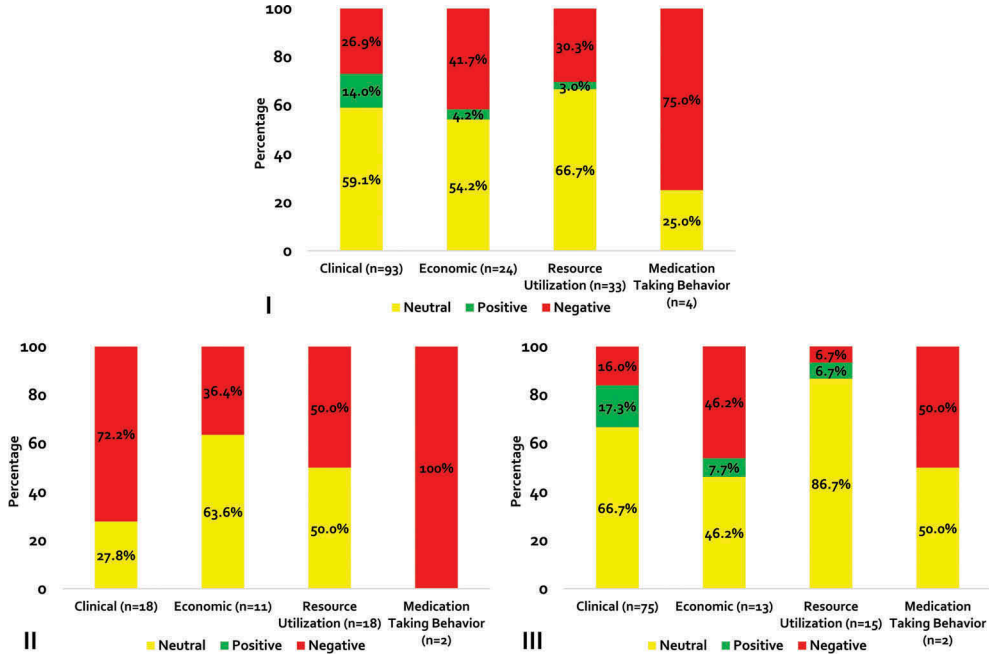

Figure 2. Direction of Outcomes in All Studies and Stratified by Non-medical Switch Categories*.

*Panel I = all studies; II = category A studies; III = category B studies

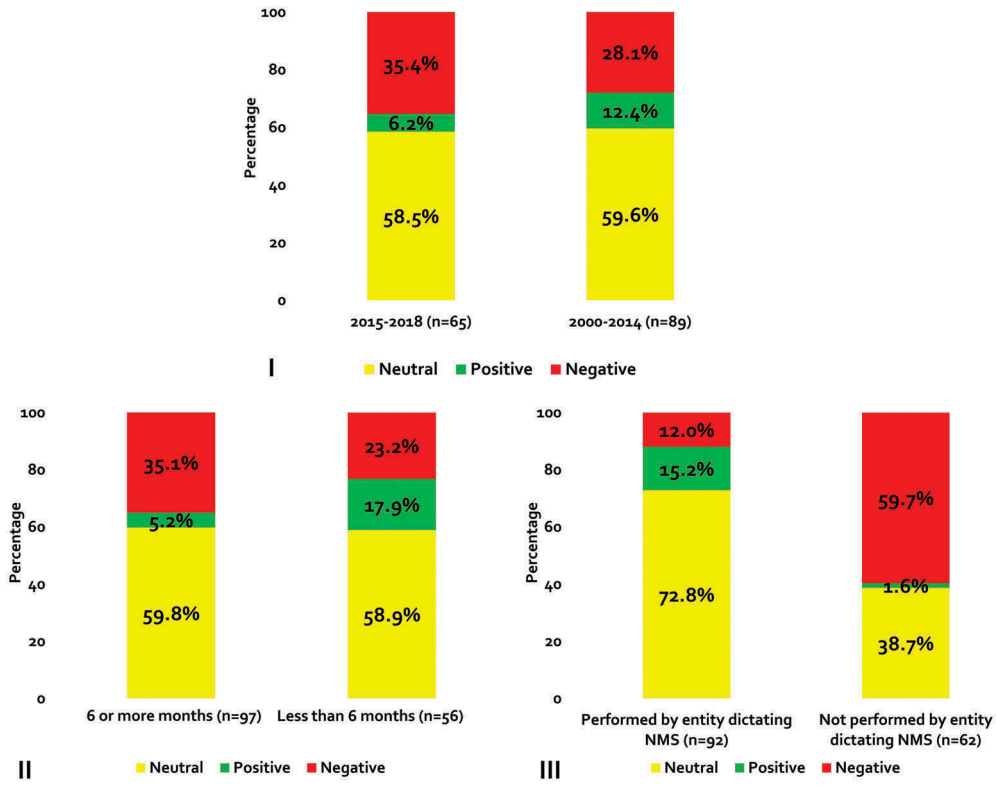

Figure 3. Direction of Outcomes Stratified by Study Subsets.

NMS = non-medical switching panel I = Stratified by publication year; II = Stratified by follow-up*; III = Stratified by whether entity performed the non-medical switch*Duration of follow-up was not reported for one outcome.

In addition to the data from studies included in this systematic review, surveys suggest both clinicians and patients view non-medical switching in a negative fashion [12,50–52]. In a survey of 569 clinicians, 77% stated that, in their opinion, it was common for the new medication to be less effective after a non-medical switch [50]. Nearly one-half of the clinicians also expressed concern regarding an increased risk of side effects with the new medication; with 37% of clinicians reporting the need to start a new medication to alleviate side effects they believed to be caused by the non-medical switch. Finally, persistence to the new medication was also a concern, with ~44% of respondents reporting at least one patient needing to switch back to their original medication. A survey of 143 patients performed by a special commission established by the Massachusetts Legislature reported on patients' impressions of non-medical switching; with 70% of respondents reporting decreased effectiveness, 86% reporting worse side effects and 48% reporting having to try multiple medications before finding an alternative that worked after a non-medical switch [51]. Nearly all (94%) of respondents noted they were in favor of legislation that would prohibit insurers from financially pressuring them to switch medications for non-medical reasons.

Non-medical switching has been addressed in guidance documents and position statements by medical, legislative and patient advocate organizations [1,2,4–7,51,53–55]. An American Medical Association (AMA) policy on standards for drug formularies and therapeutic interchange strongly discourages non-medical switching for ambulatory patients with chronic diseases [1]. The AMA has also endorsed a set of prior authorization and management reform principles [4]; which includes a principle aimed at lessening the negative impact that unanticipated formulary changes could have on patients' access to medication. This principle states that when a medication is removed from formulary after the beneficiary enrollment period is over, it should be covered for the duration of the benefit year; which at a minimum provides a buffer period for patients experiencing a non-medical switch. Reports initiated by state legislatures have also addressed non-medical switching [5,51]. A 2018 report to the Massachusetts Legislature by a commission formed to study medication switching concluded that for patients on stable medication regimens, unplanned changes can result in harm (e.g., physical, psychological and financial distress) [51]. Patient advocate organizations have released position statements on non-medical switching [6,7,53–55]. One such example, the National Diabetes Volunteer Leadership Council, emphasized their disapproval of the practice of non-medical switching and has

called for patients with well-controlled diabetes to be allowed to continue the medications that allow them to achieve adequate glycemic control [53].

Though this paper reports on an update of a prior systemic review, the present findings should not be undervalued. Both Cochrane Collaboration and AHRQ's Evidence-based Practice Center Program recommend that authors evaluate the need to update a systematic review based on several factors, including stakeholder impact (e.g., importance to guideline developers or policy makers) as well as the amount and impact of new information [19,20,56,57]. Of note, more than 40% of the endpoint data included in our updated systematic review were from studies published between 2015 and 2018; meaning the updated review added a substantial amount of new data to the previously conducted review [3]. Moreover, the rate of publication of studies evaluating non-medical switching appears to be increasing; as have the number of guidance documents and position statements on the topic [4–7,51,53–55]. This suggests the topic is considerably important to multiple stakeholder and decision-making groups. It is also worth noting that endpoints evaluated from studies published between 2015 and 2018 were more frequently negative as compared to earlier studies (i.e., 35% versus 28%). Therefore, it seems prudent to continue to closely monitor the literature describing the consequences of non-medical switching.

Our systematic review has several limitations worthy of discussion. Due to methodological characteristics of included studies, it cannot be ruled out that some 'neutral' findings would have been found to be significant if study's internal validity were improved. For example, the median follow-up duration (i.e., 6 months) for studies in the review might not be long enough to capture the most important endpoints, especially for the many cardio-metabolic conditions. While decreased control of surrogate endpoints (e.g., hemoglobin A1c, blood pressure, cholesterol levels) might be assessable within 6 months of a non-medical switch, the impact of switching on final health outcomes (e.g., microvascular complications of diabetes, myocardial infarction, stroke) would likely take >6 months to manifest [58]. This hypothesis is further supported by the fact that endpoints from studies with follow-up ≥6 months in our systematic review were more frequently negative. In addition, many studies may not have been adequately powered to show statistical differences for all endpoints assessed, and thus, would be classified as 'neutral'. For these reasons, additional and more rigorous research into the impact of non-medical switching is warranted. Next, endpoints with a large magnitude of effect received the same weight as those with a smaller magnitude of effect, and endpoints were not valued upon their corresponding clinical significance. Results were not combined statistically in a meta-analysis due to differences in the types (e.g., clinical, economic, resource utilization or medication-taking behavior) and definitions of endpoints; which would be expected to result in substantial heterogeneity if studies were meta-analyzed. We were also not able to assess endpoints in specific disease state categories, as studies assessed a heterogeneous set of conditions resulting in small study/endpoint numbers. Lastly, ~70% of included studies did not provide strong clinical data to demonstrate patients truly had stable/well-controlled disease. This limitation may bias our results towards more neutral or positive outcomes.

Conclusion

Non-medical switching in ambulatory patients was commonly associated with either negative or neutral outcomes and was seldom associated with positive ones. Among the subset of studies conducted by groups that performed/dictated the non-medical switch, outcomes were mostly neutral and positive. For this subset of studies, the possibility of reporting bias cannot be excluded. Non-medical switching was associated with mainly negative effects on clinical outcomes in patients with stable/well-controlled disease.

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Appendices

Appendix 1.

Modified Newcasttle-Ottawa Quality Assessment Scale for Evaluation of the Impact of Non-Medical Switching

Note: A study can be awarded a maximum of one star (*) for each numbered item within each category for a maximum of eight stars (*)

Selection

1) Representativeness of the 'non-medical switch' cohort
   a) truly representative of the average patient with [disease state] in the community *
   b) somewhat representative of the average patient with [disease state] in the community *
   c) selected group of users e.g., nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the comparator/non-switch cohort (i.e., patients who continued therapy or patients prior to the switch)
   a) drawn from the same community as the non-medical switch cohort *
   b) drawn from a different source
   c) no description of the derivation of the non-switch cohort
3) Ascertainment of non-medical switch
   a) secure record (e.g., patient chart or electronic health records) *
   b) structured interview *

c) assumed due to patient selection criteria
c) written self-report
d) no description

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study matched non-medical switch and non-switch patients or performs multivariable regression analyses *

Outcome

1) Assessment of outcome
   a) independent blind assessment *
   b) record linkage *
   c) self-report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes *
3) Adequacy of follow up of cohorts
   a) complete follow up – all subjects accounted for *
   b) subjects lost to follow up unlikely to introduce bias – small number lost (10%) OR description provided of those lost *
   c) follow up rate <90% and no description of those lost
   d) no statement

Other

1) Entity conducting study
   a) Study conducted by entity not involved in the non-medical switch (i.e., the entity did not dictate the switch)*

Appendix 2. Modified Newcastle-Ottawa Quality Assessment Scale Results by Non-medical Switch Category

Studies were given a star (*) or minus sign (-) in each domain if they were determined to have high or low quality, respectively.
NMS = non-medical switch

	Representativeness of the "non-medical switch" cohort	Selection of the non-switch cohort	Ascertainment of non-medical switch	Comparability of cohorts	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Entity performing study
Category A: NMS and stable/well-controlled disease								
Gibofsky, 2017	*	*	*	*	*	*	*	*
Rosenblatt, 2017	*	*	*	*	*	*	*	*
Wolf, 2017	*	*	*	*	*	*	*	*
Liu, 2015	*	*	*	-	*	*	*	*
Saseen, 2013	*	*	*	*	*	*	*	*
Kamal, 2012	*	*	*	*	*	*	*	*
Signorovitch, 2012	*	*	*	*	*	*	*	*
West, 2012	*	*	*	*	*	*	*	*
Wu, 2011	*	*	*	*	*	*	*	*
Signorovitch, 2010	*	*	*	*	*	*	*	*
Fugit, 2000	*	*	*	*	*	*	*	-
Category B: NMS with no requirement of stable/well-controlled disease								
Blonde, 2018	*	*	*	*	*	*	*	*
Flores, 2018	*	*	-	*	-	-	-	*
Naville-Cook, 2017	*	*	*	*	*	*	*	-
Boktor, 2016	*	*	*	*	*	*	*	-
Yip, 2016	*	*	*	*	*	*	*	-
Andreoli, 2015	*	*	*	*	*	*	*	-
Asias, 2015	*	*	*	*	*	*	*	-
Low, 2015	*	*	*	-	*	*	*	-
Bryant, 2013	*	*	*	*	*	*	*	-
Alemayehu, 2012	*	*	*	-	*	*	*	*
Miller, 2008	*	*	*	*	*	*	*	-
Gates, 2006	*	*	*	*	*	*	*	-
Meissner, 2006	*	*	*	*	*	*	*	-
Billups, 2005	*	*	*	*	*	*	*	-
Cheetham, 2005	*	*	*	*	*	*	*	-
Tran, 2004	*	*	*	*	-	-	-	-
Manzo, 2003	*	*	*	*	*	*	*	-
Graham, 2002	*	*	*	*	*	*	*	-
Taylor, 2001	*	*	*	*	*	*	*	-
Andrade, 2000	*	*	*	*	*	*	*	-
Clay, 2000	*	*	*	*	*	*	*	-
Good, 2000	*	*	*	*	*	*	*	-
Mamdani, 2000	*	*	*	*	*	*	*	-
Nelson, 2000	*	*	*	*	-	*	*	-
Oatis, 2000	*	*	*	*	*	*	*	-
Parra, 2000	*	*	*	*	*	*	*	-
Walters, 2000	*	*	*	*	*	*	*	-

Figure 1. Modified Newcastle-Ottawa Quality Assessment Scale Results by Non–medical Switch Category