Polypharmacy and Unplanned Hospitalizations in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Polypharmacy (PP), the prescribing of multiple drugs for an individual, is rising in prevalence. PP associates with an increased risk of adverse drug reactions (ADR) and hospital admissions. We investigated the relationship between PP, characteristics of rheumatoid arthritis (RA), and the risk of unplanned hospital admissions.

Methods. Patients from a hospital RA cohort were retrospectively analyzed. Information was collected from electronic medical records. Cox proportional hazards were used to compare hospitalization risk according to levels of PP. Admissions were adjudicated to determine whether an ADR was implicated.

Results. The study included 1101 patients; the mean number of all medications was 5. PP correlated with increasing age, disease duration, disease activity, and disability. At least 1 unplanned admission occurred for 16% of patients. Patients taking ≥ 10 medications had an adjusted HR for hospitalization of 3.1 (95% CI 2.1–4.5), compared to those taking 0–5 medications. Corticosteroid use associated with a doubling in adjusted risk of admission of 1.7 (95% CI 1.2–2.4). The most common reason for hospitalization was infection (28%). While in half of all admissions an ADR was a possible contributing factor, only 2% of admissions were found to directly result from an ADR.

Conclusion. PP is common in RA and is a prognostic marker associated with increased risk of acute hospitalizations. Our data suggest that PP may be an indicator of comorbidity burden rather than a contributing cause of a drug-related toxicity. PP should be monitored to minimize inappropriate combination of prescribed medications. PP may be a useful predictor of clinical outcomes in epidemiologic studies. (First Release October 1 2017; J Rheumatol 2017;44:1786–93; doi:10.3899/jrheum.160818)

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Prescribing is the most common intervention of the UK National Health Service (NHS) and the second-highest cost after staffing costs. Polypharmacy (PP), the prescribing of multiple drugs for an individual, is rising in prevalence in the United Kingdom. A population-based study of 300,000 patients revealed the mean number of prescribed medications increased from 3.3 in 1995 to 4.4 in 2010. This corresponded with an increase in the proportion of patients receiving 5 or more drugs climbing from 12% to 22%, and those receiving 10 or more drugs increased from 2% to 6%[1]. The reason for growing levels of PP include an aging population combined with guideline-driven management that results in patients receiving multiple concurrent medications for several conditions. PP has substantial relevance in rheumatoid arthritis (RA). Treharne, *et al* reviewed case notes for 348 patients with RA, documenting high levels of PP (mean medication count 5.4), which in turn associated with comorbid diagnoses and increasing disease duration[2].

Clinical guidelines in RA, focused on intensive treatment regimens with disease-modifying antirheumatic drugs (DMARD) and biologics, improve RA outcomes but of necessity increase PP. In addition, patients with RA have a higher burden of comorbidity than the general population,

which in turn correlates with high mortality[3,4]. Therefore, there is an increasing need for screening and management of comorbidities in RA[5] that would contribute to higher rates of PP. Explanations for the increasing prevalence of comorbidities include factors directly related to the diagnosis of RA (e.g., cardiovascular disease) or shared risk factors (e.g., smoking)[6,7,8,9].

Previous population studies have demonstrated that PP associates with an increased risk of adverse drug reactions (ADR), reduced medication adherence, and increased hospital admissions[10]. For example, 1 study estimated that 6.5% of acute medical admissions in 2 northwest UK hospitals were due to ADR[11]. A UK national survey of ADR-related hospital admissions suggested that the number of ADR admissions has increased disproportionately to the total hospital admissions. The increase in emergency admissions with a primary diagnosis of an ADR was 37% over 10 years; certainly, some may be due to improved diagnoses[12]. However, in-hospital mortality due to ADR admissions had also increased during the same period[12]. In a study of the general US population, ADR were shown to be responsible for 4.7% of all admissions[13].

Although many studies have reported on comorbidities in RA, there are few specifically examining PP in an RA population[2]. Given the advent of combination disease-modifying therapy that actively increases medication burden, understanding PP is of particular importance in RA. Here we set out to (1) evaluate the relationship between PP, RA disease characteristics, and the risk of unplanned hospital admission; and (2) to analyze the causal relationship between PP and hospitalization risk.

MATERIALS AND METHODS

Participants, data source, and PP measures. Data from an inner-city London secondary care cohort of patients with RA were used. Patients met the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League Against Rheumatology criteria for the diagnosis of RA[14,15]. The design was a retrospective cohort study. To provide contemporary data, an 18-month window of followup was selected commencing in May 2013. The hospital uses an electronic patient record for both inpatient and outpatient care, with all patient encounters recorded in a structured database. Information from all patients registered at the hospital with a consultant diagnosis of RA and under active followup was analyzed. Patient baseline characteristics were extracted from their most recent clinic visit prior to the start of the followup period including 28-joint Disease Activity Score (DAS28), disability score (Health Assessment Questionnaire; HAQ) and full list of medications (Table 1). The median time between the baseline visit and May 1, 2013, was 12 months (interquartile range 8–15).

PP information was extracted from outpatient medication charts that are updated by physicians at each hospital visit. Medications were sorted according to target organ/system with subcategories according to mode of action: drugs specific for the treatment of RA (DMARD, biologic treatment, oral corticosteroids); cardiovascular drugs; nonsteroidal antiinflammatory drugs; opioid-based analgesics and/or paracetamol; drugs affecting the respiratory, gastrointestinal, or central nervous system; medication for the treatment of diabetes mellitus; lipid/cholesterol-lowering drugs, antiplatelets/anticoagulants, dietary supplements (including calcium and vitamin D, except herbal supplements); and others (e.g., antibiotics/antimycotic/antiparasitic/antiviral drugs, hormonal treatment, antihistamines). Each patient was assigned a PP level at baseline based upon the total number of prescribed medication (including DMARD), but dietary supplements were excluded from further statistical analyses.

Acute hospitalizations and review criteria. All acute admissions to the hospital during followup were identified from the coded submissions to Hospital Episode Statistics, the central reporting system in England and Wales. Data on admissions to other hospitals were not available. Because a key aim of our study was to attempt to identify what proportion of hospitalizations were attributable to PP, as opposed to the underlying disease, detailed review of every first admission was undertaken.

Unlike the baseline drug chart, the admission medication list was drawn directly from the primary care record and verified by the hospital pharmacist. The full electronic records for each admission (admission and discharge summary, clinical notes, medication records, laboratory results) were then independently reviewed by 2 clinicians: MF (rheumatology and clinical pharmacology) and JC (general internal medicine). The data were reviewed to determine admission diagnosis, presence of an ADR, drug-drug interac-

Table 1. Characteristic and prescription strategy among patients with RA involved in the study.

	All Patients	0–5 Medications	6–9 Medications	≥ 10 Medications	p*
No. subjects, n (%)	1101 (100)	658 (59.8)	320 (29.1)	123 (11.1)	
Baseline characteristics					
Age, yrs	61.3 (16.0)	57.6 (16.3)	66.6 (14)	67.7 (13.3)	0.0001
Sex, % female	78.8	76.8	83.1	78.1	0.07
RF-positive, %	75	75.1	75.3	73.4	0.9
DAS28, mean (SD)	3.65 (1.61)	3.33 (1.60)	4.06 (1.56)	4.24 (1.38)	0.0001
HAQ, mean (SD)	1.35 (0.93)	1.02 (0.90)	1.66 (0.81)	2.04 (0.74)	0.0001
Disease duration, yrs, mean (SD)	10.42 (9.93)	9.15 (8.66)	11.93 (10.68)	13.45 (12.92)	0.0002
Smoker current/ex/never (%)	20.7/32.1/47.2	24/28.1/47.9	17.3/34.3/46.4	14.1/40.9/45	0.04
RA drugs prescribed, %					
DMARD monotherapy	45	49	42	32	0.001
DMARD dual therapy	26	24	29	27	0.19
DMARD triple therapy	8	7	8	12	0.09
Biologics	22	17	33	19	< 0.001
Corticosteroids (oral)	16	8	24	39	< 0.001

* Mantel-Haenszel test for trend. RA: rheumatoid arthritis; RF: rheumatoid factor; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drugs.

tions, and also whether the ADR was avoidable. Assessments were based on previously validated approaches[16,17,18].

Definition of ADR. An ADR is defined as any undesirable, appreciably harmful/unpleasant reaction related to the use of a drug that predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen, or withdrawal of the product[16]. Attribution of an admission to an ADR was categorized as definite/probable/possible/unlikely, in line with previously published assessment methods[16] (Supplementary Appendix 1, available with the online version of this article). The involvement of RA-related drugs in ADR across all categories was assessed (Supplementary Appendix 2, available with the online version of this article). Assessment of ADR and drug-drug interactions was guided by the STOPP criteria[19] and Beers criteria[17].

Drug-drug interactions. It is important to differentiate an ADR from a drug-drug pharmacological interaction, which in itself does not necessarily cause clinical harm. Drug-drug interactions were evaluated based on pharmaceutical, pharmacodynamic, or pharmacokinetic mechanisms. The clinical relevance of any observed interaction was graded as major, moderate, or none, as published before[18] (Supplementary Appendix 3, available with the online version of this article).

Levels of avoidability. Avoidability of ADR-related admission was classified as definitely, possibly, or unavoidable, also using previously published criteria[11,20] (Supplementary Appendix 4, available with the online version of this article).

Ethical concerns. We undertook our study as part of a locally approved service evaluation using existing data collected through routine care. All data were reviewed and analyzed by clinicians working within the department. In accordance with the Governance Arrangements for Research Ethics Committees in the United Kingdom, external ethics approval was not required.

Statistical analysis. Baseline characteristics were compared across groups using Kruskal-Wallis (for continuous variables) or chi-squared (for dichotomous variables) tests. Correlations were calculated using Spearman's correlation coefficient. Risk of hospitalization was compared between PP strata using Cox proportional hazards regression. Tests of the proportional hazards assumption were carried out with Schoenfeld residuals derived from the final models. Followup was censored at date of first admission or study end, whichever came first. A model incorporating a restricted cubic spline for PP level was constructed to describe graphically the nonlinear association between hospitalization risk with number of prescribed medications. PP levels (0–5, 6–9, or ≥ 10 medications) were defined in prior analysis based upon standardized cutoffs in the literature[1,21,22]. The analysis was performed using Stata13 and GraphPad Prism 5.

RESULTS

Prescribing strategy and association of PP with disease characteristics. The study included 1101 patients with an established diagnosis of RA, with a mean DAS28 of 3.7 ± 1.6, a mean HAQ of 1.4 ± 0.9, and disease duration of 10 years (Table 1). Overall, the mean number of prescribed medications was 5.2 ± 3.3, 60% of patients had ≤ 5 medications and 11% of patients had ≥ 10 medications. In total, 79% of patients were receiving DMARD, while 22% were receiving biologics. Out of all patients, 45% were taking DMARD monotherapy, 26% were taking dual therapy, and 8% taking triple combination DMARD therapy. The percentage taking corticosteroids was 16 (Table 1). Excluding RA treatment, the mean number of medications was 3.8 ± 3.3; the most common prescribed therapies included treatment for cardiovascular diseases (38% of all patients, comprising calcium channel blockers, 25%; diuretics, 24%; α/β adrenergic blocking agents, 17%; angiotensin II receptor antagonists, 13%; angiotensin-converting enzyme inhibitors, 6%; others, 15%), opioid-based analgesia (34%), and nonsteroidal antiinflammatory drugs (32%; Supplementary Figure 1a, available with the online version of this article).

PP increased with age ($r = 0.26$, $p < 0.001$), with 8% of patients ≤ 65 years old taking ≥ 10 medications, in contrast to 16% of patients > 65 years. Women had a higher mean number of medications (women 5.3 vs men 4.9, $p = 0.01$). There appeared to be an inverse relationship between smoking and PP, with the proportion of current smokers declining with increasing numbers of medication (mean no. medications in nonsmokers 5.6 ± 3.2; smokers 4.8 ± 2.9, $p = 0.0084$).

Measures of RA disease severity were significantly correlated with PP, with increasing PP corresponding to higher DAS28 ($r = 0.26$, $p < 0.001$), greater HAQ scores ($r = 0.45$, $p < 0.001$), and longer disease duration ($r = 0.14$, $p < 0.001$; Figure 1).

Hospitalizations. The most common reason for hospitalization was infection (28.9%), which was not significantly different across PP strata ($p = 0.24$). The most common were respiratory tract infections (15.9%), urinary tract infections (6.4%), and others (including 2 cases of septic arthritis). Neurologic conditions were responsible for 13%, trauma for 10%, and cardiovascular complications for 8% of admissions. Rheumatoid flare was implicated in only 5.8% of all acute admissions. Other causes are provided in Supplementary Figure 1b (available with the online version of this article).

PP as a predictor of acute hospitalizations. During the 18-month followup window, there were 303 admissions among 173 patients (incidence 10.8/100 patient-yrs, 95% CI 9.3–12.6). Of the 173 patients who were admitted, 63 (35%) had repeated admissions during followup. Further analysis below only included data on first admissions (n = 173).

There was a nonlinear association between increasing PP and more frequent acute hospitalizations, with an indication that the likelihood of being admitted to hospital increases sharply in patients prescribed ≥ 10 medications (Figure 2). Patients taking ≥ 10 medications had an age- and sex-adjusted HR for first hospitalization of 3.1 (95% CI 2.1–4.5) compared to those taking ≤ 5 medications. Patients taking 6–9 medications were not at significantly higher risk compared to those taking ≤ 5 medications (HR 1.0, 95% CI 0.7–1.5; Table 2).

DMARD combination strategies were not associated with increased hospitalization risk [age- and sex-adjusted HR for DMARD monotherapy 0.8 (95% CI 0.6–1.1), dual therapy HR 1.1 (95% CI 0.7–1.5), triple therapy HR 0.8 (95% CI 0.4–1.5)]. Biologic therapy did not relate to an increased risk of hospitalization [age- and sex-adjusted HR 0.8 (95% CI 0.5–1.3)]. However, use of corticosteroids was associated with a doubling of risk (HR 2.3, 95% CI 1.6–3.1) of admission (Supplementary Table 1, available with the online

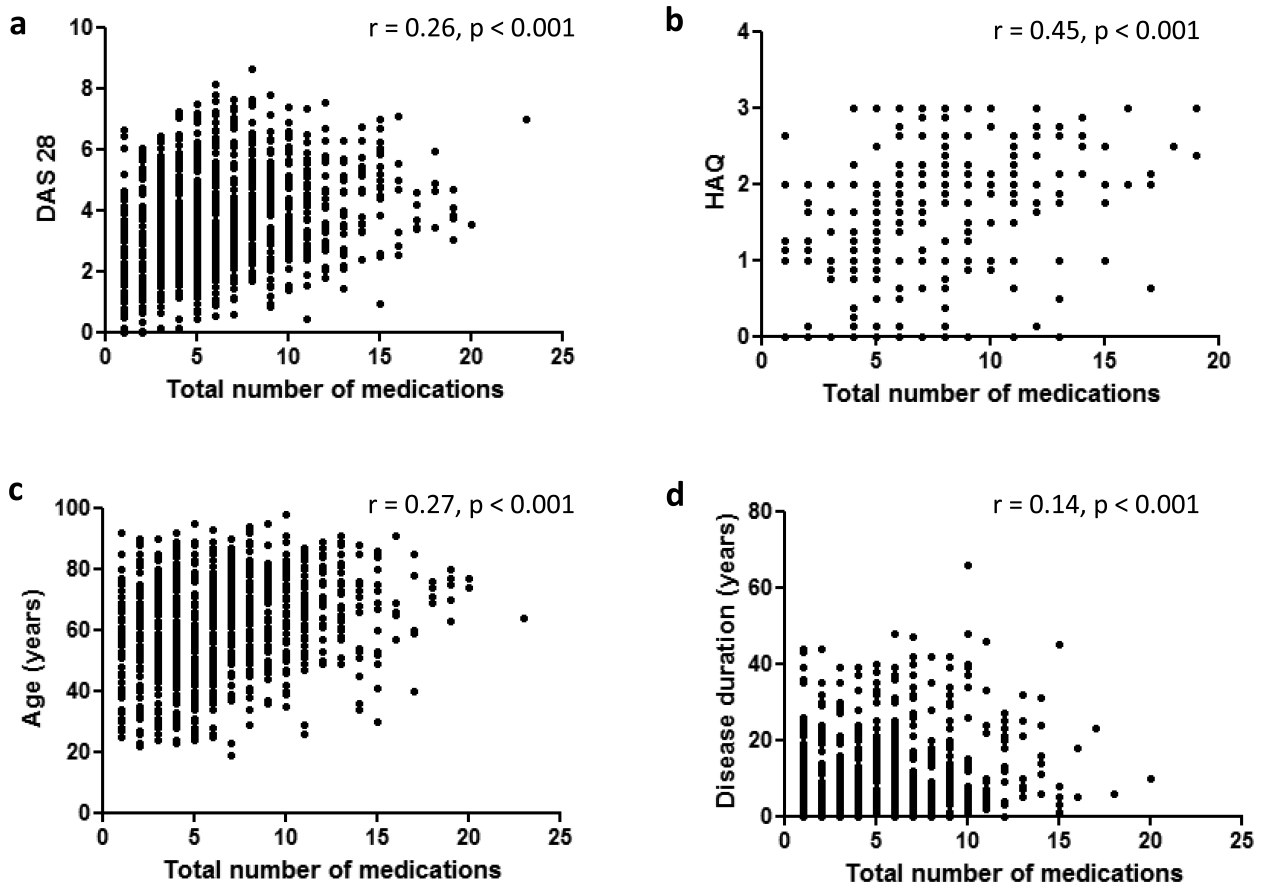

Figure 1. Association between the number of medications and DAS28 (a), HAQ (b), age (c), and disease duration (d). DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire.

version of this article). The association between corticosteroid and admission remained significant after adjusting for PP, age, and sex (HR 1.7, 95% CI 1.2–2.4).

Admissions attributed to ADR. Overall, 12 admissions (6.9% of all admissions) were considered "definitely" or "probably" attributable to an ADR (Table 3). The definite and probably ADR were distributed across all PP strata (Table 4). In half of these ADR, an RA medication was implicated in the ADR (Table 3; Supplementary Table 2, available with the online version of this article).

A substantial proportion (44.5%) of admissions were coded as "possibly" attributable to an ADR. Among the possibly attributable ADR, 40/77 (51.9%) involved an RA drug. The design of ADR classification means that completely excluding an ADR for an admission can be difficult (e.g., if a patient receiving DMARD is admitted because of infection).

Regarding which RA drugs were involved in ADR, 17.4% involved corticosteroids, 69.6% DMARD, and 26.1% biologics. Involvement of RA treatments in ADR-related admissions across PP strata is shown in Table 4.

Drug-drug interactions and avoidability of ADR-related admissions. Drug-drug interactions contributed to 10 out of 173 (11.2%) of admissions. Of these, 2 were definitely, 3 probably, and 5 possibly linked to acute admissions (Table 3). Both definite major drug-drug interactions involved anticoagulants. DMARD contributed to 4 (1 definitely involved in ADR-related admission), and biologics to 2 major drug-drug interactions. Drug-drug interactions were more frequent in patients in higher PP strata (Table 4).

After adjudication, only 2 (4.5%) of ADR-related hospitalizations were deemed definitely avoidable from a prescribing perspective; both involved predictable drug interactions with anticoagulants (Table 4).

DISCUSSION

Ours is the first study, to our knowledge, to analyze the association between PP and hospitalization specifically in patients with RA. Similarly, while data on ADR as a cause of admissions are available for the general population[11,12,23,24,25], the data for patients with RA are missing.

It is difficult to estimate the prevalence of PP in the general population given different definitions of PP and study populations analyzed (primary/secondary care, hospital

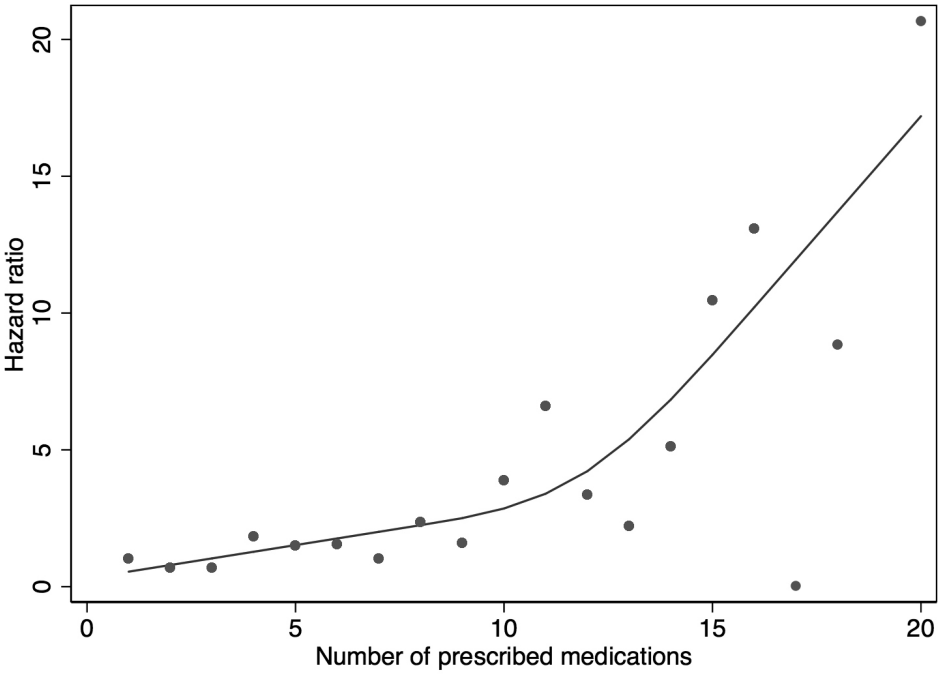

Figure 2. Increasing polypharmacy was associated with more frequent acute hospitalizations, with a marked nonlinear increase in risk in patients taking ≥ 10 medications.

Table 2. Association between polypharmacy and first acute hospitalization in patients with RA over an 18-month observation period.

	All Patients	0–5 Medications	6–9 Medications	≥ 10 Medications
Exposure time, person-yrs	1599	983	469	147
Events, n	173	75	50	48
Incidence/100 yrs (95% CI)		7.6 (6.1–9.6)	10.7 (8.1–14.1)	32.6 (24.6–43.2)
Univariable HR for hospitalization (95% CI)*		Ref	1.4 (1.0–2.0)	4.2 (2.9–6.0)
Age- and sex-adjusted HR for hospitalization (95% CI)*		Ref	1.0 (0.7–1.5)	3.1 (2.1–4.5)
Fully adjusted HR (age, sex, DAS28, disease duration; 95% CI)		Ref	0.9 (0.6–1.5)	2.6 (1.7–4.1)
HR for patients ≤ 65 yrs old, 95% CI	631	Ref	1.6 (0.9–3.1)	6.4 (3.4–11.8)
HR for patients > 65 yrs old, 95% CI	470	Ref	0.9 (0.6–1.4)	2.4 (1.5–3.7)

* Proportional hazards assumptions confirmed using Nelson-Aalen plots and Schoenfeld residuals. RA: rheumatoid arthritis; DAS28: 28-joint Disease Activity Score.

admissions, elderly population, comorbidity burden, etc.). A study using primary care data from the general population showed that almost 50% of patients aged > 20 years admitted to the hospital were prescribed at least 1 regular medication, with 25.2% receiving 1–3, 16.9% receiving 4–9, and 4.6% ≥ 10 medications[26]. Increasing numbers of regular medications are seen with female sex, older age, greater socioeconomic deprivation, and increasing multimorbidity. Cardiometabolic conditions are the most important disease cluster[22,26]. We observed that PP is common in patients with RA and is more frequently observed in women, and patients with higher disease activity, higher levels of functional impairment, and longer disease duration. None of these observations is unexpected; however, the absolute numbers of patients receiving PP is high, especially in the elderly.

Patients with higher levels of PP had a substantially greater risk of unplanned hospitalization. The risk of hospitalization was more marked in patients receiving > 10 medications. The observation that the PP and hospitalization risk was nonlinear is particularly relevant if one were to

Table 3. Analysis of relationship between adverse drug reaction (ADR) and first acute hospitalization, implicated drug-drug interactions, and avoidability of such events in all patients with rheumatoid arthritis (RA).

ADR-related admissions	Definite	Probable	Possible	Unlikely
N (%)	4 (2.3)	8 (4.6)	77 (44.5)	84 (48.6)
RA drug implicated, n (%)				
Definitely	2 (50.0)	4 (50.0)	40 (51.9)	NA
Corticosteroid implicated, n (%)				
Definitely	0 (0.0)	0 (0.0)	8 (20.0)	
Unlikely	2 (100.0)	3 (75.0)	26 (45.0)	
DMARD implicated, n (%)				
Definitely	2 (100.0)	3 (75.0)	27 (67.5)	
Unlikely	0 (0.0)	1 (25.0)	9 (22.5)	
Biologic implicated, n (%)				
Definitely	0 (0.0)	3 (75.0)	9 (22.5)	
Unlikely	2 (100.0)	1 (25.0)	29 (72.5)	
Unlikely	2 (50.0)	4 (50.0)	33 (42.9)	NA
Drug-drug interaction implicated, n (%)				
No	1 (25.0)	0 (0.0)	15 (19.5)	NA
Moderate	1 (25.0)	5 (62.5)	57 (74.0)	NA
Major	2 (50.0)	3 (37.5)	5 (6.5)	NA
Avoidability, n (%)				
Definitely	2 (50.0)	1 (12.5)	1 (1.3)	NA
Possibly	1 (25.0)	6 (75.0)	54 (70.1)	NA
Unavoidable	1 (25.0)	1 (12.5)	22 (28.6)	NA

DMARD: disease-modifying antirheumatic drug; NA: not applicable.

Table 4. Analysis of relationship between adverse drug reaction (ADR) and first acute hospitalization, implicated drug-drug interactions, and avoidability of such events in patients with RA across the polypharmacy strata.

Polypharmacy Category	All	0–5 Medications	6–9 Medications	≥ 10 Medications
N (%)	173	41 (23.7)	60 (34.7)	72 (41.6)
ADR-related admission, n (%)				
Definitely	4 (2.3)	1 (2.4)	1 (1.7)	2 (2.8)
Probably	8 (4.6)	1 (2.4)	4 (6.7)	3 (4.2)
Possibly	77 (44.5)	15 (36.6)	27 (45.0)	35 (48.6)
Unlikely	84 (48.6)	24 (58.5)	28 (46.7)	32 (44.4)
RA drug implicated, n (%)*				
Definitely	46 (51.7)	8 (47.1)	20 (62.5)	18 (45.0)
Corticosteroid	8 (17.4)	2 (25.0)	2 (10.0)	4 (22.2)
DMARD	32 (69.6)	3 (37.5)	17 (85.0)	12 (66.7)
Biologic	12 (26.1)	3 (37.5)	4 (20.0)	5 (27.8)
Unlikely	39 (43.8)	8 (47.1)	11 (34.4)	20 (50.0)
Drug-drug interaction implicated, n (%)*				
No	16 (18.0)	10 (58.8)	6 (18.8)	0 (0.0)
Moderate	63 (70.8)	7 (41.2)	22 (68.7)	34 (85.0)
Major	10 (11.2)	0 (0.0)	4 (12.5)	6 (15.0)
Avoidability, n (%)*				
Definitely	4 (4.5)	0 (0.0)	3 (9.4)	1 (2.5)
Possibly	61 (68.5)	14 (82.4)	21 (65.6)	26 (65.0)
Unavoidable	24 (27.0)	3 (17.6)	8 (25.0)	13 (32.5)

* Calculated from definitely + probably + possibly ADR-related admissions. RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drugs.

attempt to use PP as an epidemiological surrogate for comorbidity. However, at a patient level, it is important to consider why the pattern is observed. It may be that the relationship between PP and comorbidity becomes stronger above a certain point, especially because we included DMARD in the total medication count.

In addition to the relationship with comorbidity, PP may be a direct causal factor in hospitalization through ADR. It

has previously been shown that ADR account for between 0.5% and 6.5% of admissions[10,11,22]. Our estimate of definite or probable ADR-related admissions within an RA cohort was 6.9%. The low absolute numbers of definite or probable ADR precluded detailed analysis; however, it appeared that ADR were linked to specific classes of high-risk drugs (e.g., anticoagulants), whose effects may be potentiated by specific comorbidities and drug interactions that increase bleeding risk, rather than absolute numbers of medication.

Some ADR can be avoidable (hazardous prescribing), but we observed very few such events. In contrast, many ADR occur in the setting of appropriate prescribing. In the context of RA, most clinicians now accept that the infectious risks of DMARD are far outweighed by the beneficial effect upon RA, with the knowledge that untreated RA is a far more hazardous state.

Our analyses, with specific consideration for RA drugs within the context of PP, were reassuring, with no demonstrated apparent association between more intensive DMARD strategies, including use of biologics, and hospitalization risk. There was, however, a 2-fold higher rate of hospitalization among corticosteroids users. These could have been prescribed either for treatment of RA or another comorbidity, increasing the risk of hospitalization; however, owing to lack of information on comorbidities in our study we are unable to draw conclusions on an indication. Although DMARD contribute to PP, it may be that an adequate control of disease activity is protective against admission. An alternative explanation is that there may be channeling bias, with healthier patients more likely to be prescribed combination DMARD or biologic treatment strategies, while clinicians adopt more cautious approaches (perhaps favoring steroids) for patients with complex background comorbidity.

Drug-drug interactions were documented in 82% of admissions, but only 11% were considered of clinical significance. As expected, patients in higher PP strata were more exposed to drug-drug interactions compared to patients in the lowest strata. However, it is important to acknowledge that simple assessments of drug-drug interaction may dramatically overestimate risk of clinically relevant problems[27].

PP may be a useful proxy tool (unlike the calculation of indices of comorbidity) to adjust for confounding by comorbidity in epidemiologic analyses and identify patients at high risk of hospitalizations for targeted risk management. Comorbidity indices have been used to measure and weigh the overall burden of comorbidities and have been used in predicting mortality[28], but not in predicting acute admissions. Different methods have been used to predict risk of emergency admissions, which took into account demographic, lifestyle, laboratory, and clinical variables, and chronic disease[23,29]. These tools appear complicated for stratification of acute admissions in daily practice, and routinely collected PP data may act as a useful surrogate. Whether this is the case could be investigated in further studies.

A key strength of this research is the use of real-world data — electronic medical records (EMR) and emphasis on collecting defined core data generated in day-to-day situations rather than typically selective controlled trials. The growing use of EMR and emphasis on collecting defined core data in specific diseases such as RA makes it easier to use real-world data sources in research. Using routinely collected data to evaluate the effect of PP has both strengths and limitations. The growing use of EMR and routine data sources may help overcome issues of generalizability that limit trials.

Limitations of our study include misclassification biases, unmeasured confounding, missing data, and censorship. Clinicians may be less thorough in recording medication in routine care than in formal clinical studies, resulting in reduced data quality or missing data. Because we relied upon the secondary care record of patient-prescribed medication, it is likely that we were unaware of some medications patients were receiving (including over-the-counter medications), and our measurement of PP is likely an underestimate. However, for all hospitalizations, a pharmacist undertakes medicine reconciliation directly with primary caregivers and, therefore, we were able to compare an actual number of prescribed medications with our own record of PP at baseline. Among patients admitted with an infection, the mean number of medications recorded in our baseline record was 7.0 (SD 4.0), compared to a mean number of medications of 8.9 (SD 4.3) at the time of admission. While some of this increase may genuinely represent additional medications prescribed between baseline and the date of admission, it also provides some estimate of the extent of missing information on baseline medication.

Regarding misclassification of exposure, recall bias was avoided by using electronically recorded prescription data, but precise information on dispensing and adherence was unavailable. Indeed, it was inaccuracy in comorbidity coding that initiated the authors' interest in PP as a measure. It is notable that when we compared the medicine reconciliation data from pharmacists at the time of admission, the extent of medication misclassification was reassuringly low. However, a number of nuances, such as transient episodic use of medications, may have been missed. A further limitation is that it is likely that some patients had admissions at other hospitals. We hypothesize that additional admission to other inner-city Trust hospitals may have contributed to the higher number of drug-related admissions. Therefore, our estimates of hospitalization rate can be considered conservative because we will have underestimated the true rate. However, there is no reason to think that this bias would have affected patients at different levels of PP differentially. We attempted to reduce confounding by design and analysis (multivariable adjustments on age and sex); however, residual confounding likely remains (e.g., socioeconomic and other factors). The complexity of medications in some cases and the lack of full

medical records made the judgment of appropriate or inappropriate prescribing impossible.

Our study found PP to be associated with increased risk of acute hospitalizations, particularly for those taking > 10 medications. There are 2 likely drivers for these effects: PP as a contributing cause of an increased drug-related toxicity or PP as an indicator of greater comorbidity burden. It is unclear in what manner PP influences adverse outcomes and our data suggest the risk may be nonlinear. However, PP should undoubtedly be closely monitored to minimize potentially inappropriate combinations of prescribed medications. These observations also support the hypothesis that PP may be a useful clinical tool: a simple, novel, and readily measurable predictor of clinical outcomes. Undoubtedly, more research and further validation studies need to be done before firm conclusions can be drawn. However, patients exposed to higher levels of PP represent a population of particular relevance to the modern NHS: these patients are typically excluded from clinical trials and, therefore, data regarding drug efficacy in the setting of PP are lacking[27].

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. BMC Med 2015;13:74.
2. Treharne GJ, Douglas KM, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. Musculoskeletal Care 2007;5:175-90.
3. Gabriel SE. Why do people with rheumatoid arthritis still die prematurely? Ann Rheum Dis 2008;67 Suppl 3:iii30-4.
4. Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2011;25:469-83.
5. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis 2014;73:62-8.
6. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690-7.
7. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology 2011;50:124-31.
8. Mercer LK, Davies R, Galloway JB, Low A, Lunt M, Dixon WG, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. Rheumatology 2013;52:91-8.
9. Solomon DH, Kremer J, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010;69:1920-5.
10. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. Pharmacoepidemiol Drug Saf 2010;19:901-10.
11. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004;329:15-9.
12. Wu TY, Jen MH, Bottle A, Molokhia M, Aylin P, Bell D, et al. Ten-year trends in hospital admissions for adverse drug reactions in England 1999-2009. J R Soc Med 2010;103:239-50.
13. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998;279:1200-5.
14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010; 69:1580-8.
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
16. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356:1255-9.
17. By the American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227-46.
18. Lea M, Rognan SE, Koristovic R, Wyller TB, Molden E. Severity and management of drug-drug interactions in acute geriatric patients. Drugs Aging 2013;30:721-7.
19. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing 2015;44:213-8.
20. Hallas J, Harvald B, Gram LF, Grodum E, Brosen K, Haghfelt T, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. J Intern Med 1990;228:83-90.
21. Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med 2015;175:827-34.
22. Vyas A, Pan X, Sambamoorthi U. Chronic condition clusters and polypharmacy among adults. Int J Family Med 2012;2012:193168.
23. Hippisley-Cox J, Coupland C. Predicting risk of emergency admission to hospital using primary care data: derivation and validation of QAdmissions score. BMJ Open 2013;3:e003482.
24. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One 2009;4:e4439.
25. Patel H, Bell D, Molokhia M, Srishanmuganathan J, Patel M, Car J, et al. Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998-2005. BMC Clin Pharmacol 2007;7:9.
26. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol 2014;77:1073-82.
27. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. BMJ 2015;350:h1059.
28. Yurkovich M, Avina-Zubieta JA, Thomas J, Gorenchtein M, Lacaille D. A systematic review identifies valid comorbidity indices derived from administrative health data. J Clin Epidemiol 2015;68:3-14.
29. Donnan PT, Dorward DW, Mutch B, Morris AD. Development and validation of a model for predicting emergency admissions over the next year (PEONY): a UK historical cohort study. Arch Intern Med 2008;168:1416-22.