Scandinavian Journal of Primary Health Care, 2009; 27: 153–159

informa
healthcare

ORIGINAL ARTICLE

The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients

A modified Delphi study

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Abstract

Objective. To establish a clinically relevant list with explicit criteria for pharmacologically inappropriate prescriptions in general practice for elderly people ≥70 years. *Design*. A three-round Delphi process for validating the clinical relevance of suggested criteria (n = 37) for inappropriate prescriptions to elderly patients. *Setting.* A postal consensus process undertaken by a panel of specialists in general practice, clinical pharmacology, and geriatrics. *Main outcome measures.* The Norwegian General Practice (NORGEP) criteria, a relevance-validated list of drugs, drug dosages, and drug combinations to be avoided in the elderly (≤70 years) patients. *Results.* Of the 140 invited panellists, 57 accepted to participate and 47 completed all three rounds of the Delphi process. The panellists reached consensus that 36 of the 37 suggested criteria were clinically relevant for general practice. Relevance of three of the criteria was rated significantly higher in Round 3 than in Round 1. At the end of the Delphi process, a significant difference between the different specialist groups' scores was seen for only one of the 36 criteria. *Conclusion*. The NORGEP criteria may serve as rules of thumb for general practitioners (GPs) related to their prescribing practice for elderly patients, and as a tool for evaluating the quality of GPs' prescribing in settings where access to clinical information for individual patients is limited, e.g. in prescription databases and quality improvement interventions.

Key Words: *Drug safety, Delphi technique, explicit criteria, elderly, family practice, general practice, prescribing*

While being the major consumers of modern drug therapy due to their disproportional higher chronic and degenerative pathologies, the elderly are at the same time particularly vulnerable to adverse drug reactions (ADRs) and other drug-related problems. Depending on the criteria used, between 14% and 25% of all prescriptions issued to elderly outpatients have been judged to represent potential pharmacological inappropriateness [1–3]. Such criteria are usually drug- or disease-oriented, do generally not include patients' clinical state, comorbidity or preferences, and are usually based on reviews, opinions, or consensus among experts. In health services research, two consensus methods are commonly adopted: (1) the Delphi process, and (2) the nominal group technique (i.e. expert panels) [4]. The Delphi method is accomplished by two or three postal rounds with a questionnaire completed by a panel of experts. After each round, the results are analysed and fed back to respondents including their own previous ratings as compared with panel averages, offering the opportunity to reconsider previous responses, until consensus is reached [5,6].

Identifying which drugs should be avoided for elderly patients may be a matter of controversy because evidence derived from randomized

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(Received 3 August 2008; accepted 20 April 2009)

ISSN 0281-3432 print/ISSN 1502-7724 online
DOI: 10.1080/02813430902992215

Published criteria for disclosing potentially inappropriate prescriptions for elderly patients usually do not address the general practice setting.

- A clinically validated list should be established including drugs, drug dosages, and drug combinations generally not to be used for safety reasons.
- The list may be used for quality assessments and audit to identify areas in need of quality improvements.
- The list may also serve as a supporting tool during medication list reviews and during the prescribing process.

controlled trials (RCTs) is either limited or non-existent [6]. During the last decade, assessments of inappropriate prescriptions to elderly patients have commonly been based on the Beers criteria [7,8], last updated by Fick and co-workers in 2003 [9]. These criteria concern inappropriateness of single drugs or drug dosage with or without consideration of diagnosis, and are principally formulated for the US setting. They include drugs unavailable or only rarely used in Norway, and do not include potentially harmful combinations of drugs. Thus, there is a need for criteria of relevance for Norwegian general practice and comparable settings [10].

The aim of this study was to generate a list comprising explicit criteria for pharmacological inappropriate prescriptions to elderly ($\geq$ 70 years) patients in general practice. Furthermore, it was sought to validate the clinical relevance of the list by a panel of clinical specialists utilizing a three-round Delphi process.

Material and methods

Four of the authors (SR, JS, OS, and TBW), of whom three are professors in general practice (JS), clinical pharmacology (OS), and geriatrics (TBW) respectively, generated a list of 37 explicit criteria based on among others the Beers criteria with updates [7–9], Swedish recommendations [11], previous and present Norwegian studies [12], more recent evidence from the literature [13–34], and experiences from their own clinical practices. The criteria for pharmacological inappropriateness were related to patients $\geq$70 years in general practice. Of the 37 criteria, 19 targeted particular drugs, two addressed drug dosage limits, while the rest represented a selection of drug combinations.

In late 2006, 140 physicians were invited to participate in a Delphi consensus process regarding the clinical relevance of the suggested criteria. They included all members of the Norwegian Association for Clinical Pharmacology (n = 33), a random group of Norwegian GP specialists (n = 55), and 41 specialists in geriatrics representing about half the members of the Norwegian Geriatrics Society.

The panellists were sent a questionnaire in which they were asked to score the clinical relevance for general practice of each of the 36 criteria on a 100 mm Visual Analogue Scale (VAS), according to the statement: "In general practice, the prescription rate of this item should be as low as possible for individuals $\geq$70 years", from 0 (highly irrelevant) to 100 (highly relevant). The participants were encouraged to comment on the suggested criteria and on their own ratings. In Round 2, the participants gave a new score for all criteria based on feedback from Round 1, including their own previous ratings, mean ratings for the group with standard deviations, and the comments given to each indicator. This procedure was repeated in Round 3.

Inappropriateness

For each criterion, the panellists' median score served as a measure for the central opinion in the group. Inappropriateness was considered to be clinically relevant if the median score fell within the upper third (66.7–100.0) range, and irrelevant in the lower third (0–33.3) range.

Agreement

For each criterion, the inter-quartile range (IQR) was calculated. Prior to the process, agreement had been defined to exist if the IQR fell within any one-third range of the scale. Disagreement was considered to exist if the IQR outstretched the lower or upper third of the scale. When there was agreement and the median rating fell within the 33.3–66.7 range, it was considered equivocal, and individual comments together with scores were used to decide the relevance of the criterion. In the assessment of the dynamic process of the Delphi study, we used the standard deviation (SD) of the mean as a measure for the development of agreement throughout the three rounds [35]. Statistical significance was set at $p \leq 0.05$.

Results

Of the 140 invited physicians, 57 responded positively and completed the first round, 50 participated in the second, and 47 (33.5 %) completed all three

rounds. This article is based on data from the 47 panellists participating in all three rounds: 14 clinical pharmacologists, 17 geriatricians, and 16 GPs.

The panel agreed that 36 of 37 suggested criteria for pharmacological inappropriateness were clinically relevant for patients $\geq$70 years in general practice. Twenty-one explicit criteria (ECs) concerned single drugs and dosages (Tables I and III), and 15 ECs concerned drug combinations to be avoided (Tables II and IV). Only one of the suggested recommendations, namely to avoid the combination of erythromycin or clarithromycin and digitoxin, did not meet the conditions for being included on the list (median score of 65.3 and IQR 20.0).

During the three rounds of the Delphi process, the panel held a stable opinion for 33 of the remaining 36 criteria whereas their mean rating increased significantly during the process for three (ECs 12, 31, and 32) of them (see Tables III and IV). From first to third round, increasing agreement was seen for 30 of the criteria (i.e. all criteria except ECs 1, 3, 14, 22, 25, and 29). The mean standard deviation, as a measure of disagreement, decreased from 22.3 in Round 1 to 15.6 in Round 2 and 14.9 in Round 3. Concurrent prescription of a non-steroid anti-inflammatory drug (NSAID) and a selective serotonin reuptake inhibitor (SSRI) (EC 29) achieved the lowest relevance rating score, while the panellists gave the highest score for concurrent prescription of three or more psychotropic drugs (EC 36). Highest agreement was seen for ECs 11 (flunitrazepam), 14 (carisoprodol), and 36 (simultaneous use of three or more psychotropic drugs). The lowest agreement concerned concurrent use of an NSAID and a glucocorticoid, and the combination of an NSAID and an SSRI (see Table IV).

Over the three Delphi process rounds, the geriatrician group showed highest internal agreement, while most disagreement was seen among the GPs. The consequences of not using the benzodiazepine hypnotic flunitrazepam (EC 11) in the elderly was judged (mean score in last round with 95% confidence interval) differently by clinical

Table I. Norwegian General Practice (NORGEP) explicit criteria (EC) for single drugs and drug dosages considered potentially pharmacological inappropriate for patients $\geq$70 years in general practice.

EC no.	NORGEP criteria	Comments*
1.	Amitriptyline	Tricyclic antidepressants: Anticholinergic effects, risk of impaired cognitive function[13,34] (EC 1–4)
2.	Doxepine	Tricyclic antidepressants are cardiotoxic (EC 1–4)
3.	Clomipramine	
4.	Trimipramine	
5.	Chlorpromazine	First-generation low potency antipsychotics: Anticholinergic effects, extrapyramidal effects (EC 5–8)
6.	Chlorprothixene	
7.	Levomepromazine	
8.	Prochlorperazine	Often prescribed for dizziness despite lack of documentation (EC 8)
9.	Diazepam	Long-acting benzodiazepines: Prolonged elimination half-life, risk of accumulation, muscular weakness, falls and fractures[21,23,24,30] (EC 9–11)
10.	Nitrazepam	
11.	Flunitrazepam	
12.	Oxazepam >30 mg/24 h	High doses of benzodiazepines and benzodiazepine-like agents: Risk of muscular weakness, falls and fractures[21,23,24,30] (EC 12–13)
13.	Zopiclone >7.5 mg/24 h	
14.	Carisoprodol	Centrally acting muscle relaxants: Anticholinergic effects, risk of addiction (EC 14)
15.	Dextropropoxyphene	Analgesics: More toxic than its comparators (EC 15)
16.	Theophylline	Pulmonary drugs: Risk of arrhythmias, No documented effect in COPD (EC 16)
17.	Sotalol	Cardiovascular drugs: Risk of arrhythmias, poor safety record (EC 17)
18.	Dexchlorfeniramine	First-generation antihistamines: Anticholinergic effects, prolonged sedation (EC 18–21)
19.	Promethazine	
20.	Hydroxyzine	
21.	Alimemazine (trimeprazine)	

Notes: *Numbers in superscript refer to the reference list while numbers in parentheses refer to EC numbers for which the statement is valid.

Abbreviations: NSAID = non-steroid anti-inflammatory drug; ACE = angiotensin converting enzyme; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; COPD = chronic obstructive pulmonary disease; ARB = angiotensin receptor blocker.

Table II. Norwegian General Practice (NORGEP) explicit criteria (EC) for drug combinations considered potentially pharmacologically inappropriate for patients >70 years in general practice.

EC no.	NORGEP criteria	Comments*
22.	Warfarin+NSAID	Warfarin combinations: Increased risk of intestinal bleeding[19] (EC 22)
23.	Warfarin+ofloxacin or ciprofloxacin	Increased risk of bleeding due to inhibition of warfarin metabolism[16, 19] (EC 23–24)
24.	Warfarin+erythromycin or clarithromycin	
25.	Warfarin+SSRI	Increased risk of bleeding due to a direct platelet-inhibiting effect[16] (EC 25)
26.	NSAID (or coxib)+ACE inhibitor (or ARB)	NSAIDs combinations: Increased risk of renal failure[32,33] (EC 26)
27.	NSAID+diuretic	Reduced effect of diuretics[18] (EC 27)
28.	NSAID+glucocorticoid	Increased risk of intestinal bleeding. Risk of fluid retention[27](EC 28)
29.	NSAID+SSRI	Increased risk of gastrointestinal bleeding[15, 25] (EC 29)
30.	Erythromycin or clarithromycin+statin	Other combinations: Increased risk of adverse effects of statins, including rhabdomyolysis, due to inhibition of statin metabolism[17,26,29]. Highest risk for simvastatin and lovastatin (EC 30)
31.	ACE inhibitor+potassium or potassium-sparing diuretic	Increased risk of hyperkalemia[22,31] (EC 31)
32.	Fluoxetine or fluvoxamine+ TCA	Increased risk of adverse effects of TCAs due to inhibition of TCA metabolism[20] (EC 32)
33.	Beta blocker+cardioselective calcium antagonist	Increased risk of atrioventricular block and myocardial depression[14] (EC 33)
34	Diltiazem+lovastatin or simvastatin	Increased risk of adverse effects of statins, including rhabdomyolysis, due to inhibition of statin metabolism[26] (EC 34)
35	Erythromycin or clarithromycin+carbamazepine	Increased risk of adverse effects of carbamazepine due to inhibition of its metabolism[20] (EC 35)
36.	Concomitant prescription of three or more drugs within the groups centrally acting analgesics, antipsychotics, antidepressants and/or benzodiazepines	Increased risk of muscular weakness, falls, fractures and cognitive impairment[24] (EC 36)

Notes: *Numbers in superscript refer to the reference list while numbers in parentheses refer to EC numbers for which the statement is valid.

Abbreviations: NSAID =non-steroid anti-inflammatory drug; ACE =angiotensin converting enzyme; SSRI =selective serotonin reuptake inhibitor; TCA =tricyclic antidepressant; COPD =chronic obstructive pulmonary disease; ARB =angiotensin receptor blocker.

pharmacologists, 88.6 (82.4 to 94.8), and GPs 97.8 (95.3 to 100.0).

The tendency towards more agreement within the panel during the three rounds is illustrated by the increasing average relevance scores for all 36 criteria (78.0, 81.0, and 82.3, respectively), and the decrease in corresponding SDs (22.3, 15.6, and 14.9, respectively).

Only for five of the criteria (ECs 1, 3, 22, 24, and 26) did the agreement decrease slightly from Round 2 to Round 3 as illustrated by an SD increase by an average of 6.1. But here also the panellists' agreement increased from the first to the third round.

Discussion

The main outcome of this study is a clinically validated list of 36 explicit criteria for potentially inappropriate prescriptions to patients ≥70 years in general practice, the Norwegian General Practice (NORGEP) Criteria. The aim of the process was not to address all possible drug-related problems, but rather to generate a feasible list that should include some of the most relevant prescriptions to be avoided for elderly patients for safety reasons.

That 36 out of 37 suggested criteria were judged to be clinically relevant may reflect thorough preparation by the expert panel in selecting cases to be validated in the Delphi process.

The criterion that in relative terms obtained lowest agreement was the statement that GPs should avoid using an NSAID along with an SSRI due to the added risk of gastrointestinal bleeding [15]. Here, the lowest degree of agreement was found among GP specialists (SD 30.1 in Round 3), while the clinical pharmacologists tended to agree more (SD 13.1 in Round 3). The fact that the evidence for this interaction was fairly new, and maybe also because its clinical magnitude had been questioned [36], may partly explain this variable rating.

The Delphi technique is flexible and enables a large number of experts to contribute to a relatively inexpensive process without geographic limitations. The anonymity in the postal-based Delphi process prevents dominance by high-profile experts, which might represent a problem in a face-to-face setting.

Table III. Norwegian General Practice (NORGEP) explicit criteria (EC) for single drugs and drug dosages considered potentially pharmacologically inappropriate for patients >70 years in general practice. Validating the clinical relevance of the criteria by a specialist panel during a three-round postal Delphi process: mean scores[1] during third round with inter-quartile range (IQR)[2] and standard deviation (SD), and mean change in score from first to third round.

ECno.	NORGEP criteria	Rating score in Round 3 Mean (Median)	IQR, Round 3	SD, Round 3	Change in opinion from Round 1 to 3 Mean (95 % CI)
1.	Amitriptyline	85.3 (85,0)	12.0	11.9	2.7 (–1.6 to 6.9)
2.	Doxepine	84.7 (85,0)	11.0	12.6	3.0 (–0.8 to 6.9)
3.	Chlomipramine	85.4 (85,0)	12.0	11.5	0.1 (–3.8 to 2.1)
4.	Trimipramine	84.1 (80,0)	11.0	11.5	0.2 (–3.9 to 4.3)
5.	Chlorpromazine	83.9 (85,0)	10.0	13.0	2.7 (–2.3 to 7.6)
6.	Chlorprothixene	82.5 (80,0)	10.0	14.1	1.4 (–2.8 to 5.6)
7.	Levomepromazine	87.3 (90,0)	20.0	13.4	0.1 (–3.6 to 3.4)
8.	Prochlorperazine	81.3 (80,0)	15.0	12.0	1.7 (–2.9 to 6.4)
9.	Diazepam	83.7 (80,0)	10.0	11.5	4.4 (–0.7 to 9.6)
10.	Nitrazepam	84.8 (85,0)	10.0	11.3	4.3 (–0.3 to 8.9)
11.	Flunitrazepam	92.3 (92,0)	10.0	8.4	1.1 (–2.2 to 4.5)
12.	Oxazepam >30 mg/24 h	87.2 (90,0)	20.0	10.8	3.8 (0.6 to 10.6)
13.	Zopiclone >7.5 mg/24 h	88.4 (90,0)	15.0	11.8	0.5 (–2.1 to 3.1)
14.	Carisoprodol	94.0 (95,0)	10.0	7.2	2.9 (–0.7 to 6.5)
15.	Dextropropoxyphene	88.5 (90,0)	15.0	12.6	3.4 (–1.7 to 8.5)
16.	Theophylline	72.4 (74,0)	21.0	17.8	5.1 (–0.8 to 11.1)
17.	Sotalol	72.2 (70,0)	10.0	17.4	6.1 (–0.9 to 13.2)
18.	Dexchlorpheniramine	88.0 (80,0)	15.0	13.1	0.8 (–2.3 to 4.1)
19.	Promethazine	81.4 (80,0)	17.0	13.2	1.5 (–2.1 to 5.3)
20.	Hydroxyzine	80.9 (80,0)	15.0	13.2	2.3 (–3.5 to 8.2)
21.	Alimemazine (trimeprazine)	76.9 (75,0)	20.0	16.6	3.0 (–2.6 to 8.8)

Notes: [1]Rating scores are given on visual analogue scales (VAS) from 0 to 100 (0 = complete disagreement, 100 = complete agreement). [2]Consensus is by definition achieved if the inter-quartile range (IQR) falls within any one-third of the rating scale.
Abbreviations: NSAID = non-steroid anti-inflammatory drug. ACE = angiotensin converting enzyme. SSRI = selective serotonin reuptake inhibitor. TCA = tricyclic antidepressant. ARB = angiotensin receptor blocker. 95% CI = 95% confidence interval.

Table IV. Norwegian General Practice (NORGEP) explicit criteria (EC) for drug combinations considered potentially pharmacologically inappropriate for patients >70 years in general practice. Validating the clinical relevance of the criteria by a specialist panel during a three-round postal Delphi process: mean scores[1] during third round with inter-quartile range (IQR)[2] and standard deviation (SD), and mean change in score from first to third round.

ECno.	NORGEP criteria	Rating score, Round 3 Mean (Median)	IQR, Round 3	SD, Round 3	Change in opinion from Round 1 to 3 Mean (95 % CI)
22.	Warfarin + NSAID	88.0 (90,0)	15.0	16.0	5.3 (–2.2 to 12.8)
23.	Warfarin + ofloxacin or ciprofloxacin	71.3 (70,0)	16.0	16.4	4.1 (–2.9 to 11.2)
24	Warfarin + erythromycin or clarithromycin	74.3 (75,0)	10.0	17.9	3.1 (–4.0 to 10.4)
25	Warfarin + SSRI	69.8 (70,0)	27.0	17.3	1.0 (–7.6 to 5.6)
26.	NSAID (or coxib) + ACE inhibitor (or ARB)	80.1 (80,0)	15.0	16.8	2.6 (–2.2 to 7.5)
27.	NSAID + diuretic	81.0 (80,0)	15.0	16.3	3.0 (–1.3 to 7.5)
28.	NSAID + glucocorticoid	78.3 (80,0)	10.0	19.0	4.9 (–0.5 to 10.3)
29.	NSAID + SSRI	68.0 (65,0)	20.0	19.6	6.2 (–1.8 to 14.3)
30.	Erythromycin or clarithromycin + statin	74.4 (75,0)	10.0	13.7	1.5 (–3.7 to 6.8)
31.	ACE inhibitor + potassium or potassium-sparing diuretic	86.1 (85,0)	12.0	15.4	4.7 (0.4 to 9.0)
32.	Fluoxetine or fluvoxamine + TCA	87.4 (90,0)	18.0	11.2	10.7 (2.7 to 18.7)
33.	Beta blocker + cardioselective calcium antagonist	88.3 (90,0)	10.0	11.0	0.7 (–4.7 to 6.1)
34.	Diltiazem + lovastatin or simvastatin	77.8 (75,0)	15.0	10.5	0.8 (–5.9 to 4.4)
35.	Erythromycin or clarithromycin + carbamazepine	78.2 (80,0)	5.0	11.1	1.9 (–1.7 to 5.5)
36.	Concomitant use of three or more psychotropic drugs[3]	95.0 (95,0)	10.0	5.1	4.4 (–0.8 to 11.1)

Notes: [1]Rating scores are given on visual analogue scales (VAS) from 0 to 100 (0 = complete disagreement, 100 = complete agreement). [2]Consensus is by definition achieved if the inter-quartile range (IQR) falls within any one-third of the rating scale. [3]Centrally acting analgesics, antipsychotics, antidepressants, and/or benzodiazepines.
Abbreviations: NSAID = non-steroid anti-inflammatory drug. ACE = angiotensin converting enzyme. SSRI = selective serotonin reuptake inhibitor. TCA = tricyclic antidepressant. ARB = angiotensin receptor blocker. 95% CI = 95% confidence interval.

The Delphi technique, like any other structured communication method, has its limitations. The method has been criticized to the extent that it forces consensus by not allowing participants to discuss the issues [37]. Following the feedback from previous rounds, some panellists changed their views, which reinforced the group's opinion. This increase in agreement may thus be the result of constructive feedback during the process, but it is also possible that the panellists conformed to the view held by the majority [35]. The numerous comments (which were subsequently forwarded to the others) suggest that the panellists participated actively in the study and that the feedback process worked satisfactory. Questions have also been raised that the selection of panellists in Delphi studies may be biased (e.g. their numbers and level of homogeneity), and that this may affect the outputs [38]. A panel that includes few participants will definitely decrease the reliability of the Delphi process [39]. We do not think that these concerns are valid for our study because our panel included more participants than commonly adopted and our panel was also constituted by three different clinical specialist groups [7].

To assess the *clinical* relevance of the proposed criteria, we recruited clinical specialists from the three most relevant clinical specialties: general practice, clinical pharmacology, and geriatrics. We succeeded well in obtaining balanced participation from the three specialist groups. We cannot, however, rule out the fact that the acceptance to participate in the process to some extent was influenced by an a priori positive attitude to the proposed criteria. Also contributing to the internal validity of the process is that more than four out of five who accepted, equally distributed between the three specialties, completed all three rounds. A 17% dropout rate is in line with corresponding figures seen in other Delphi studies [5,40].

The main outcome of this study, the NORGEP criteria, is a relevance-validated 36-item list of explicit criteria for potential pharmacological inappropriateness for GPs' prescribing practice to patients $\geq$70 years. However, explicit drug-based criteria for prescription appropriateness, like this one, should be used with some caution for assessing prescription performance by individual physicians. We recommend that the criteria should primarily be utilized at group level for identifying problem areas in need of quality improvements [41]. Even though the panellists were asked to address the GP setting, we also think that the NORGEP criteria may be useful in other settings too, for example in nursing homes. Also, individual GPs may find the list useful as a supporting tool during medication list reviews for own patients and in their decision-making process when prescribing drugs to elderly patients [42]. Furthermore, the Delphi technique used here may also be suitable for revising and updating the NORGEP criteria in the future.

Acknowledgements

The authors would like to thank all specialists who participated in the three Delphi rounds.

Competing interests: The authors declare no competing interests.

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