

## Sex Differences in Inappropriate Drug Use: a Register-Based Study of Over 600,000 Older People

Kristina Johnell, Gunilla Ringbäck Weitoft, and Johan Fastbom

Potentially inappropriate drug use is an important cause of nonadherence, adverse drug reactions, hospitalization, and mortality in the elderly population.<sup>1-5</sup> However, these negative outcomes are believed to be largely preventable and avoidable by more appropriate drug prescribing.<sup>1,4</sup> Several studies have observed a higher rate of inappropriate drug use in elderly women than in elderly men,<sup>6-16</sup> although few have focused explicitly on sex differences.<sup>7</sup> Also, educational level (a measure of socioeconomic status)<sup>17</sup> has been associated with both polypharmacy and inappropriate drug use in the elderly population,<sup>13,18</sup> which could explain sex differences in inappropriate drug use. However, few studies about sex differences in inappropriate drug use have controlled for educational level. In addition, many previous studies have been severely limited by small and selected study samples without enough statistical power to analyze individual drugs. Therefore, we wanted to investigate the association between sex and inappropriate drug use after adjustment for educational level in a large nationwide population of older people.

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**BACKGROUND:** Several studies have observed a higher rate of inappropriate drug use in elderly women than in elderly men, although few have focused explicitly on sex differences. Also, educational level (a measure of socioeconomic status) has been associated with both polypharmacy and inappropriate drug use in the elderly population, which could explain sex differences in inappropriate drug use.

**OBJECTIVE:** To investigate whether sex is associated with inappropriate drug use in a large general population of older people, after adjustment for age, socioeconomic status (ie, educational level), and comorbidity (ie, number of drugs).

**METHODS:** We conducted an analysis of data on sex, age, dispensed drugs, and education for people aged 75–89 years who were registered in the Swedish Prescribed Drug Register between July and October 2005 (N = 645,429). The main outcome measures were the filling of prescriptions for anticholinergic drugs or long-acting benzodiazepines, concurrent use of 3 or more psychotropic drugs, and potentially serious drug–drug interactions.

**RESULTS:** Potentially inappropriate drug use was more common in women (24.6%) than in men (19.3%). More women than men were exposed to all types of inappropriate drug use, except for potentially serious drug–drug interactions. Logistic regression analysis showed that women were more likely to be exposed to potentially inappropriate drug use than were men (OR 1.24; 95% CI 1.23 to 1.26) after adjustment for age, education, and number of drugs (used as a proxy for comorbidity). In particular, female sex was highly associated with inappropriate psychotropic use (eg, long-acting benzodiazepines: adjusted OR [OR<sub>adjusted</sub>] 1.45; 95% CI 1.42 to 1.49; >3 psychotropic drugs: OR<sub>adjusted</sub> 1.50; 95% CI 1.47 to 1.53). In contrast, women had a lower probability of potentially serious drug–drug interactions than did men (OR<sub>adjusted</sub> 0.81; 95% CI 0.80 to 0.83).

**CONCLUSIONS:** Inappropriate drug use in the elderly should be monitored separately for women and men. Our results suggest that neither socioeconomic status nor comorbidity seem to explain sex differences in inappropriate drug use. Future research in other large study populations is needed for investigation of other explanations behind these sex differences.

**KEY WORDS:** drug register, elderly, inappropriate drug use, sex differences, Sweden.

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Author information provided at the end of the text.

ty indicators for evaluation of drug therapy in older people. These indicators are quantitative measures based on international literature on the quality of drug use in the elderly population.<sup>9,19</sup> We analyzed 4 drug-specific quality indicators that have previously been applied to register-based data<sup>9,20,21</sup>: anticholinergic drugs, long-acting benzodiazepines, concurrent use of 3 or more psychotropic drugs, and potentially serious drug–drug interactions.<sup>4</sup> Anticholinergic drugs can cause urinary retention, impaired functional status, and confusion in older people.<sup>22,23</sup> Therefore, most anticholinergic drugs should be considered inappropriate for the elderly.<sup>23</sup> Long-acting benzodiazepines have prolonged half-lives in the elderly (sometimes days) and can therefore cause excessive sedation, cognitive impairment, and falls.<sup>23,24</sup> Concurrent use of 3 or more psychotropic drugs is a refined measure of polypharmacy and may raise concerns regarding the total sedative load, adverse drug reactions, and poor adherence.<sup>25–27</sup> Further, drug–drug interactions have been related to adverse drug reactions and hospitalizations in the elderly.<sup>4,28–32</sup> Older people are more frail and sensitive to adverse drug reactions and also consume more drugs than do other age groups; therefore, they are the group most exposed to drug–drug interactions.<sup>33</sup>

There are great possibilities in Sweden for research on potentially inappropriate drug use by using the Swedish Prescribed Drug Register. The register provides data with nationwide coverage on all individuals exposed to dispensed drugs. By using the unique personal identification number, it is possible to link data on individual drug use with other register data (eg, education, income, mortality, hospitalization). The Swedish Prescribed Drug Register represents one of the largest population-based pharmacoepidemiologic databases in the world.<sup>9,34</sup>

The aim of this study was to investigate whether sex is associated with inappropriate drug use (ie, the prescription of anticholinergic drugs or long-acting benzodiazepines, concurrent use of  $\geq 3$  psychotropic drugs, potentially serious drug–drug interactions) in a large general population of older people after adjustment for age, education, and number of drugs.

## Methods

### STUDY POPULATION

The Swedish Prescribed Drug Register contains individual-based data on all dispensed prescriptions to the whole population of Sweden (about 9 million inhabitants). The data collection is administered by the state-owned National Corporation of Swedish Pharmacies and is then transferred to the National Board of Health and Welfare.<sup>34</sup>

The Swedish Prescribed Drug Register for the period July–October 2005 was individually linked by personal

identification numbers to the national education register, which is updated yearly by Statistics Sweden and includes information on the highest level completed of formal education of each Swedish citizen aged 16–74 years.<sup>35</sup> In Sweden, the maximum quantity of drugs prescribed is a 90-day supply. Therefore, it was believed that a study period of 4 months should include the filling of most prescriptions. The information on education level was collected from the years 1990, 1997, 2000, and 2004, and information was available for those aged 20–74 years. Consequently, information in the education register for individuals aged 90 years or older in 2005 was not complete; these persons were therefore excluded.<sup>36</sup> Also, 2.3% (15,357/660,786) of the individuals aged 75–89 years with missing education data were excluded. Finally, nonidentifiable data on age, sex, dispensed drugs during the 4-month period, and education were analyzed for 387,951 women and 257,478 men aged 75–89 years.

### DEFINITIONS

The dispensed drugs were classified according to the Anatomical Therapeutic and Chemical classification system, as recommended by the World Health Organization.<sup>37</sup> Assessment of potentially inappropriate drug use was based on 4 quality indicators developed by the National Board of Health and Welfare: filling of prescriptions for at least one anticholinergic drug (eg, antihistamines, urinary antispasmodics, nonselective monoamine reuptake inhibitors, low-potency neuroleptics, anticholinergic antiparkinsonian drugs, anticholinergic antiemetics),<sup>20</sup> filling at least one prescription for a long-acting benzodiazepine (ie, diazepam, flunitrazepam, nitrazepam), concurrent use of 3 or more psychotropic drugs (ie, neuroleptics, anxiolytics, hypnotics/sedatives, antidepressants), and at least one potentially serious drug–drug interaction.<sup>9,19</sup> Inappropriate drug use was defined as exposure to at least 1 of the 4 quality indicators.<sup>9</sup> Potentially serious drug–drug interactions were classified according to the Swedish system developed by Sjöqvist, which is published in the Swedish Physicians' Desk Reference.<sup>38</sup> The drug–drug interactions are divided into 4 levels of clinical relevance: type A (probably no clinical relevance), type B (clinical relevance not yet established), type C (potentially clinically relevant), and type D (potentially serious). We focused on potentially serious drug–drug interactions.<sup>38,39</sup> Examples of type D drug–drug interactions are aspirin plus a nonsteroidal anti-inflammatory drug, aspirin plus warfarin, and potassium-sparing diuretics plus potassium.<sup>9,39</sup>

Education level was coded into 3 groups according to the Swedish educational system: low (<9 y of education [used as reference group]), medium (9–12 y), and high (>12 y).<sup>40</sup> Age was categorized into 3 groups: 75–79 (reference), 80–84, and 85–89 years. Number of drugs dis-

pensed during the 4-month study period, used as a proxy for comorbidity, was divided into 4 categories: 1–4 (reference group), 5–9, 10–14, and 15 or more drugs.<sup>41</sup> The study was approved by the ethical board in Stockholm (Dnr 2006/948-31).

### STATISTICAL ANALYSIS

Both univariate and multivariate logistic regression analysis were used to investigate whether sex was associated with inappropriate drug use. In the univariate (unadjusted) analyses, only sex was entered as the explanatory variable, without adjustment for other variables. In the multivariate (adjusted) analysis, adjustment was made for age, education level, and number of drugs. The results are shown as odds ratios with 95% confidence intervals. SPSS 14.0 for Windows (SPSS Inc., Chicago, IL) was used for the analyses.

### Results

The mean  $\pm$  SD age for women was  $81.2 \pm 4.1$  years; for men it was  $80.6 \pm 3.9$  years. On average, women were prescribed  $7.0 \pm 4.7$  drugs and men were prescribed  $6.4 \pm 4.5$  drugs during the 4-month study period. In general, men had a higher educational level than women (Table 1).

Overall, 24.6% of the women and 19.3% of the men were exposed to potentially inappropriate drug use (Table 2). A higher percentage of women than men were exposed to all types of inappropriate drug use, except for potentially serious drug–drug interactions. The 3 most frequently used anticholinergic drugs were urinary antispasmodics, nonselective monoamine reuptake inhibitors, and hydroxyzine. In addition, 2 or more anticholinergic drugs were used by 1.3% of the women and 0.9% of the men. All 3 long-acting benzodiazepines were more commonly used by women, and a larger percentage of women than men

used 3 or more psychotropic drugs concurrently. Potentially serious drug–drug interactions, however, were slightly more common among men than among women. Aspirin (used by women: 33.5%, men: 41.5%) and warfarin (used by women: 5.6%, men: 9.1%) were involved in the 3 most common potentially serious drug–drug interactions.

The univariate logistic regression analysis (Table 3) showed that women were more likely to be exposed to po-

**Table 2.** Inappropriate Drug Use in Study Population<sup>a</sup>

Parameter	Women, n (%)	Men, n (%)
$\geq 1$ Indications of inappropriate drug use	95,613 (24.6)	49,787 (19.3)
<b>Types of inappropriate drug use</b>		
Anticholinergic drugs	33,658 (8.7)	16,397 (6.4)
urinary antispasmodics	11,350 (2.9)	6,356 (2.5)
nonselective monoamine reuptake inhibitors	8,775 (2.3)	2,646 (1.0)
hydroxyzine	7,225 (1.9)	3,790 (1.5)
Long-acting benzodiazepines	25,859 (6.7)	11,080 (4.3)
diazepam	10,431 (2.7)	4,886 (1.9)
flunitrazepam	10,084 (2.6)	4,257 (1.7)
nitrazepam	6,159 (1.6)	2,289 (0.9)
$\geq 3$ Psychotropic drugs	35,882 (9.2)	14,523 (5.6)
<b>Potentially serious drug–drug interactions</b>		
Aspirin plus NSAIDs	16,140 (4.2)	11,059 (4.3)
Aspirin plus warfarin	1,303 (0.3)	1,850 (0.7)
Warfarin plus NSAIDs	1,349 (0.3)	1,397 (0.5)

NSAIDs = nonsteroidal antiinflammatory drugs.  
<sup>a</sup>N = 387,951 women and 257,478 men.

**Table 3.** Logistic Regression for Inappropriate Drug Use in Women Compared with Men in Study Population<sup>a</sup>

Parameter	Odds Ratio (95% CI)	
	Unadjusted	Adjusted <sup>b</sup>
$\geq 1$ Indications of inappropriate drug use	1.36 (1.35 to 1.38)	1.24 (1.23 to 1.26)
Anticholinergic drugs	1.40 (1.37 to 1.42)	1.29 (1.27 to 1.32)
urinary antispasmodics	1.19 (1.15 to 1.23)	1.13 (1.09 to 1.17)
nonselective monoamine reuptake inhibitors	2.23 (2.13 to 2.33)	2.06 (1.97 to 2.15)
hydroxyzine	1.27 (1.22 to 1.32)	1.11 (1.07 to 1.16)
Long-acting benzodiazepines	1.59 (1.55 to 1.62)	1.45 (1.42 to 1.49)
diazepam	1.43 (1.38 to 1.48)	1.30 (1.26 to 1.35)
flunitrazepam	1.59 (1.53 to 1.65)	1.45 (1.39 to 1.50)
nitrazepam	1.80 (1.71 to 1.89)	1.63 (1.55 to 1.71)
$\geq 3$ Psychotropic drugs	1.70 (1.67 to 1.74)	1.50 (1.47 to 1.53)
Potentially serious drug–drug interactions	0.93 (0.91 to 0.95)	0.81 (0.80 to 0.83)
aspirin plus NSAIDs	0.97 (0.94 to 0.99)	0.88 (0.86 to 0.91)
aspirin plus warfarin	0.47 (0.43 to 0.50)	0.42 (0.39 to 0.45)
warfarin plus NSAIDs	0.64 (0.59 to 0.69)	0.60 (0.56 to 0.65)

<sup>a</sup>N = 645,429.  
<sup>b</sup>Adjusted for age, education, and number of drugs.

Parameter	Women, n (%)	Men, n (%)
Age (y)		
75–79	152,793 (39.4)	114,733 (44.6)
80–84	140,293 (36.2)	92,336 (35.9)
85–89	94,865 (24.5)	50,409 (19.6)
Education		
low (<9 y)	221,322 (57.0)	134,515 (52.2)
medium (9–12 y)	132,844 (34.2)	88,264 (34.3)
high (>12 y)	33,785 (8.7)	34,699 (13.5)
Dispensed drugs, n		
1–4	137,555 (35.5)	104,768 (40.7)
5–9	152,612 (39.3)	99,759 (38.7)
10–14	68,808 (17.7)	38,366 (14.9)
$\geq 15$	28,976 (7.5)	14,585 (5.7)

tentially inappropriate drug use than were men; this association remained after adjustment for age, educational level, and number of drugs. In particular, female sex was highly associated with inappropriate psychotropic use of nonselective monoamine reuptake inhibitors, which have anticholinergic effects; long-acting benzodiazepines; and concurrent use of 3 or more psychotropic drugs. In contrast, women had a lower probability of potentially serious drug–drug interactions than did men.

## Discussion

In our nationwide population of older people, about 25% of the women and 19% of the men were exposed to potentially inappropriate drug use. Female sex was associated with a higher likelihood of inappropriate drug use,<sup>7-10,12,13,15,16</sup> even after adjustment for age, educational level, and number of drugs. Thus, socioeconomic status, as measured by educational level, did not explain the sex differences found in this study. Another explanation could be that women more often report worse health conditions and more often use healthcare services than do men.<sup>42,43</sup> However, we did control for number of drugs, which is related to both comorbidity and healthcare visits.<sup>41</sup> Thus, this explanation is less likely to entirely explain the sex differences in inappropriate drug use observed in this study.

Possible mechanisms behind sex differences in inappropriate drug use may be marital status and type of housing, which should be explored in future studies of this topic. Also, there may be differences between women and men regarding disease manifestation, ways of communicating, and healthcare provider–patient interaction.<sup>43</sup> This possible explanation might be related to our finding that women seem to be particularly prone to inappropriate psychotropic use, as shown by the strong correlations between sex and psychotropic drugs with anticholinergic properties, long-acting benzodiazepines, and concurrent use of 3 or more psychotropic drugs. This finding is in concordance with a study that found that psychotropic and anticholinergic drugs contribute to the higher rates of inappropriate drug use in older women.<sup>7</sup> The authors concluded that targeted efforts to avoid these types of drugs in elderly women may help to reduce overall rates of inappropriate drug use. Another study reported that inappropriate central nervous system drugs contribute to the higher odds for inappropriate drug use in women and stated that interventions could target a more appropriate selection of these drugs to eliminate a large portion of inappropriate drug use and reduce its higher risk for women.<sup>16</sup> Psychiatric diseases should be treated with safer alternatives to inappropriate drugs, regardless of sex.

In contrast to the other measures of inappropriate drug use, we found that potentially serious drug–drug interactions were more common among men than women. The

higher use of aspirin and warfarin by men probably explains this finding, as these drugs were involved in the 3 most common potentially serious drug–drug interactions. Similar findings of fewer potential drug–drug interactions among women have been reported in other studies.<sup>39,44,45</sup> However, some studies have not found any sex differences.<sup>46-48</sup> In fact, the opposite scenario has been reported, in which women are more likely to be exposed to drug–drug interactions than men.<sup>49</sup> Yet, these studies have not focused solely on the elderly and have not been adjusted for age, educational level, and number of drugs.

Only information from people aged 75–89 years who were registered in the Swedish Prescribed Drug Register between July and October 2005 and had complete data was used, which corresponded to about 89% (645,429/725,035) of the Swedish population of that age in 2005. However, the excluded 15,357 people aged 75–89 years who had missing data on educational level had a mean age of 81.9 years, 66% were women, and 24% had inappropriate drug use. In other words, these excluded people did not extensively differ from the study population.

Further, the Swedish Prescribed Drug Register does not include data on over-the-counter drugs, herbal drugs, drugs used in hospitals, and drugs supplied from drug storerooms that are sometimes used in nursing homes; this may lead to an underestimation of inappropriate drug use. The analyses of inappropriate drug use were not adjusted for other measurements of socioeconomic status or comorbidity that may act as confounders. Nevertheless, educational level is a strong determinant of employment and income,<sup>17</sup> and the number of dispensed drugs may be regarded as a proxy for comorbidity.<sup>41</sup> Finally, potentially inappropriate drug use is not the same as actual inappropriate drug use. For the individual patient, a drug regarded as inappropriate by definition may sometimes be justified.<sup>19</sup>

Inappropriate drug use in the elderly should be monitored separately for women and men. Our results suggest that neither socioeconomic status nor comorbidity seem to explain sex differences in inappropriate drug use. Future research in other large study populations is needed in order to investigate other explanations behind these sex differences.

The healthcare system should provide health care on equal terms and there is an increasing awareness of equal rights to safe and effective health care. Efforts should be made to address sex differences in inappropriate drug use in order to obtain safe drug therapy regardless of sex. Ideally, sex differences in inappropriate drug use should be considered in interventions for improvement of the quality of drug therapy in the elderly population. In particular, there are opportunities to reduce women's higher level of inappropriate use of psychotropic drugs.

**Kristina Johnell** MScPharm PhD, Junior Research Fellow, Aging Research Center, Karolinska Institutet, Stockholm, Sweden



**Gunilla Ringbäck Weitoft** PhD, Investigator, Centre for Epidemiology, National Board of Health and Welfare, Stockholm

**Johan Fastbom** MD PhD, Associate Professor, Aging Research Center

**Reprints:** Dr. Johnell, Aging Research Center, Karolinska Institutet, Gävlegatan 16, 113 30 Stockholm, Sweden, fax 46 (0)8 690 68 89, Kristina.Johnell@ki.se

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Diferencias en el uso Inadecuado de Fármacos Entre los Sexos: Un Estudio Basado en un Registro de Sobre 600,000 Personas Mayores

K Johnell, GR Weitof, y J Fastbom

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EXTRACTO

**TRASFONDO:** Varios estudios han observado un índice más alto en el uso inadecuado de fármacos (UIF) en mujeres mayores que en hombres mayores, aunque pocos estudios se han concentrado explícitamente en las diferencias entre los sexos. En adición, el nivel educativo (una medida del estado socioeconómico) ha sido asociado tanto con la polifarmacia como con el UIF en la población de personas mayores, lo que podría explicar las diferencias en el UIF entre los sexos.

**OBJETIVO:** Investigar si el sexo está asociado con el UIF, después de hacer ajustes por la edad, el estado socioeconómico (ie, nivel educativo), y co-morbilidades (i.e. número de fármacos) en una población general grande de personas mayores.

**MÉTODOS:** Se realizó un análisis de datos en base al registro, del sexo, la edad, los fármacos despachados, y la educación, de personas mayores entre las edades de 75–89 años de edad registradas en el Registro de Fármacos Prescritos Sueco durante los meses de julio–octubre de 2005 (n = 645,429). Las medidas principales de los resultados del UIF fueron el despacho de prescripciones de fármacos anticolinérgicos, benzodiazepinas de acción prolongada, el uso concurrente de ≥3 fármacos psicotrópicos y las interacciones de fármaco–fármaco potencialmente serias.

**RESULTADOS:** Potencialmente, el UIF fue más común en mujeres (24.6%) que en hombres (19.3%). Más mujeres que hombres estuvieron expuestas a todos los tipos de UIF con la excepción de interacciones fármaco–fármaco

potencialmente serias. Un análisis de regresión logística mostró que las mujeres tuvieron más probabilidad de ser expuestas al potencial UIF que los hombres (OR 1.24; 95% CI 1.23 y 1.26), después de un ajuste por la edad, la educación y el número de fármacos (usado como sustituto de co-morbilidades). En particular, el sexo femenino fue asociado en gran manera con el uso inadecuado de psicotrópicos (ej. benzodiazepinas de acción prolongada: OR<sub>ajustado</sub> 1.45; 95% CI 1.42 y 1.49 y ≥3 fármacos psicotrópicos: OR<sub>ajustado</sub> 1.50; 95% CI 1.47 y 1.53). En contraste, las mujeres tuvieron una probabilidad más baja de interacciones fármaco–fármaco potencialmente serias que los hombres (OR<sub>ajustado</sub> 0.81; 95% CI 0.80 y 0.83).

**CONCLUSIONES:** El UIF en los ancianos debe ser monitoreado por separado en hombre y mujeres. Los resultados de este estudio sugieren que ni el estado socioeconómico ni las co-morbilidades parecen explicar las diferencias en el UIF entre los sexos. Investigaciones futuras en otras poblaciones grandes de estudio son necesarias para investigar otras explicaciones más allá de estas diferencias entre los sexos.

Traducido por Brenda R Morand

Différence Entre les Hommes et les Femmes dans l'Utilisation de Médicaments Non Appropriés: Une Étude d'un Registre National Chez plus de 600,000 Sujets Ages

K Johnell, GR Weitof, et J Fastbom

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RÉSUMÉ

**OBJECTIF:** Évaluer s'il existe une différence entre les hommes et les femmes dans l'utilisation de médicaments non appropriés, après un ajustement pour l'âge, le statut socio-économique et la présence de co-morbidité (par exemple le nombre de médicaments) chez une population âgée.

**MÉTHODES:** Les auteurs ont évalué les données chez des sujets âgés entre 75 et 89 ans à partir d'un registre national des médicaments prescrits en Suède et comprenant des données sur le genre, l'âge, les médicaments dispensés, et le niveau d'éducation des personnes âgées entre juillet et octobre 2005 (n = 645,429). Les issues primaires de l'utilisation des médicaments non appropriés étaient la prise de médicaments anticholinergiques, les benzodiazépines à longue demi-vie, la prise concomitante de plus de 3 psychotropes et le potentiel de développer des interactions médicamenteuses de type médicaments–médicaments.

**RÉSULTATS:** L'utilisation de médicaments non appropriés était plus souvent rencontré chez les femmes (24.6%) que chez les hommes (19.3%). Plus de femmes que d'hommes étaient exposés à tous les types de médicaments non appropriés, excepté pour les interactions médicamenteuses potentiellement sérieuses. Une analyse de régression logistique a démontré que les femmes étaient plus à risque d'être exposé à un médicament potentiellement non approprié que les hommes (OR 1.24; 95% CI 1.23 à 1.26), après un ajustement pour l'âge, le niveau d'éducation et le nombre de médicaments (utilisé comme indicateur de co-morbidité). Les femmes étaient particulièrement à risque élevé de recevoir un agent psychotrope (eg. benzodiazépines à action prolongée: OR<sub>ajustée</sub> 1.45; 95% CI 1.42 à 1.49 et ≥3 psychotropes: OR<sub>ajustée</sub> 1.50; 95% CI 1.47 à 1.53). Cependant, les femmes avaient un risque moins élevé de présenter une interaction médicamenteuse potentiellement dangereuse. (OR<sub>ajustée</sub> 0.81; 95% CI 0.80 à 0.83).

**Conclusions:** L'utilisation des médicaments non appropriés devrait être évalué séparément chez les femmes et les hommes. Les auteurs mentionnent que le statut socio-économique et la présence de co-morbidité n'expliquent pas les différences entre les hommes et les femmes quant à l'utilisation de médicaments non appropriés.

Traduit par Louise Mallet