The elimination half-life of benzodiazepines and fall risk: two prospective observational studies

Oscar J. de Vries, Geeske Peeters, Petra Elders, Caroline Sonnenberg, Majon Muller, Dorly J. H. Deeg, Paul Lips

Abstract

Background: the STOPP criteria advise against the use of long-acting benzodiazepines (LBs).
Objective: to study whether LBs are associated with a higher fall risk than short-acting benzodiazepines (SBs) (elimination half-life ≤ 10 h).
Methods: we used base-line data and prospective fall follow-up from the Longitudinal Aging Study Amsterdam, a longitudinal cohort study including 1,509 community-dwelling older persons (Study 1) and from a separate fall prevention study with 564 older persons after a fall (Study 2). Time to the first fall after inclusion and number of falls in the first year after inclusion were the primary endpoints.
Results: both in Study 1 and Study 2 the use of SBs was associated with time to the first fall, hazard ratio (HR) 1.62 (95% CI: 1.03–2.56) and HR 1.64 (95% CI: 1.19–2.26), respectively. LBs were not significantly associated with time to first fall, HR 1.40 (0.85–2.31) and HR 1.08 (0.72–1.62). In both studies, the use of SBs was also associated with number of falls, odds ratio (OR) 1.28 (95% CI: 1.01–1.61) and OR 1.37 (95% CI: 1.10–1.70). LBs were not significantly associated with number of falls, OR 1.23 (0.96–1.57) and 1.10 (0.82–1.48).
Conclusions: the use of SBs is not associated with a lower fall risk compared with LBs. The use of both SBs and LBs by old persons should be strongly discouraged.

Keywords: aged, accidental falls, benzodiazepines, sedatives, adverse drug events, older people

Introduction

Falls and fall-related complications are a major problem in older persons. One-third of the older population experiences at least one fall each year, 15% falls two times or more each year. Ten percent of falls leads to serious consequences such as fractures, requiring medical treatment [1–4].

Previous research has shown that psychotropic medications, such as benzodiazepines and tricyclic antidepressants, are associated with increased fall risk [5, 6]. Moreover, their use has been shown to be not only associated with increased risk of injurious falls, but also with increased risk of hip fractures [7, 8]. Apart from the loss of function and quality of life attributable to medication-related falls, the financial impact on society is considerable [9].

Although most studies applied adjustment for co-morbid conditions, confounding by indication cannot be ruled out as a partial explanation of the association of psychotropic drug use with increased fall risk. Persons with pre-existing conditions that increase the risk of
Injuries falls are significantly more likely to receive a new prescription for a benzodiazepine [10]. Furthermore, only a few studies have used prospectively obtained data on falls; in most pharmacoepidemiological studies retrospective data on falls or (hip) fractures were used as primary endpoints [6].

The STOPP (Screening Tool of Older Persons’ potentially inappropriate Prescriptions) is an explicit medicine review tool that is rapidly gaining importance in geriatric medicine. Among the prescriptions that are active in the central nervous system, the tool deems the use of ‘long-term’ (i.e. >1 month), long-acting benzodiazepines’ potentially inappropriate because of the risks of prolonged sedation, confusion, impaired balance and falls [11]. Despite this advice, several aspects of the fall risk increasing properties of psychotropic drugs are uncertain. Mainly due to methodological difficulties the debate on the influence of the elimination half-life of benzodiazepines on fall risk is yet undecided. The use of long-acting benzodiazepines (LBs) has been found to be associated with greater fall and fracture risk than short-acting benzodiazepines (SBs) [12, 13]. Other studies found opposite results or found the dosage to be a more important fall risk factor than the elimination half-life [14, 15]. In these studies, the maximum elimination half-life of benzodiazepines of agents that were considered ‘short-acting’ was 24 h. However, benzodiazepines with a half-life shorter than 10 h may have a different influence on fall risk than those with a longer elimination half-life. This effect may have been overlooked by clustering these very short-acting benzodiazepines with those with an elimination half-life of up to 24 h. Because the benzodiazepines with an elimination half-life of 10 h or less are less likely to accumulate when taken one to three times a day, we hypothesised that they are associated with a lower fall risk than benzodiazepines with a longer half-life.

In two separate prospective studies among non-institutionalised old persons with a low to intermediate and a high risk of falls, respectively, we have addressed the association between the use of benzodiazepines with short and long elimination half-life and accidental falls.

**Methods**

**Study 1**

**Study design and population**

Data for this study were collected in the context of the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in autonomy and well-being in the ageing population in the Netherlands [16]. The sampling and data collection procedures have been described in detail elsewhere [17].

The present study was performed using a subsample of the LASA cohort, including 1,509 respondents out of 1,720 eligible, who participated in the second data collection cycle of LASA (1995/1996), were born aged 65 years and older and were living in the community (Figure 1).

**Study 2**

**Study design and population**

This study is a prospective observational part of a secondary fall prevention study in older persons with a 1-year follow-up. The design of this study was published in detail elsewhere [22]. The study sample consisted of persons of 65 years and over, who consulted the emergency department of the VUmc and conducted according to the principles of the Helsinki declaration.

**Assessment of falls**

Participants were asked to record falls every week for 3 years on a ‘fall calendar’ and to mail the calendar page to the research institute at 3-month intervals [18].

A fall was defined as ‘an unintentional change in position resulting in coming to rest at a lower level or on the ground’ [19].

**Assessment of medication use and co-morbidity**

During the home visit, the names and instructions of both prescription and over-the-counter medication were recorded directly from the container. All medications were classified according to the Anatomical Therapeutical Chemical (ATC) coding system [20].

During the interview the presence of seven major categories of chronic somatic diseases (lung diseases, cardiac diseases, vascular diseases, joint diseases, malignant diseases, diabetes mellitus and stroke) and psychiatric diseases, both in the past and present were assessed [21].

![Flow-chart of the inclusion in Study 1.](image)
into a medium high risk and a very high-fall-risk group [19]. The very high-risk group was randomised into a usual care (n = 111) and an intervention group (n = 106). Because the intervention in this trial did not significantly alter the fall risk, the data of all 564 participants could be evaluated for the current observational study.

All participants signed informed consent, and the study was approved by the Medical Ethics Committee of the VUmc and conducted according to the principles of the Helsinki declaration.

Assessment of falls, medication use and co-morbidity

All participants were visited at their homes by a trained interviewer within 3 months after the presenting fall. During this home visit, medication use and co-morbidity was assessed and the participants were asked to record falls applying the same procedure as in Study 1.

Both studies

Short and long-acting benzodiazepines

Benzodiazepines and benzodiazepine-like drugs were initially identified using the first five digits of the ATC code: N05BA, N05CD and N05CF. Using their full seven digit ATC code, all benzodiazepines and benzodiazepine-like drugs with a lower limit of their estimated elimination half-life of 10 h or less were considered short acting (Table 1, see Supplementary data available in Age and Ageing online). In Study 2 the diazepam dose equivalent of all benzodiazepines and benzodiazepine-like drugs was calculated [24]. In Study 1, this was not reliable because an estimate of the frequency of use in case of use ‘as needed’ was not systematically recorded.

Data-analysis

The association between time to the first fall in the year after inclusion and use of SBs and LBs was analysed with Cox regression analysis. Log-binomial regression was performed to analyse the association between benzodiazepine use and number of falls in 1-year follow-up. This analysis was performed for 0 versus 1 or more falls and for 0 or 1 fall versus 2 or more falls. In both studies, the analyses were adjusted for relevant confounders: age, gender, number of chronic diseases and additionally for intervention in Study 2.

Additionally, in Study 2 the association of the diazepam dose equivalent with time to first fall could be analysed with Cox regression analysis. The association of a weekly diazepam dose equivalent of >35 mg with the number of falls was tested with log-binomial regression analysis.

The analyses were performed using SPSS 17.0.0 (SPSS, Inc., 2008).

Results

Study 1

The participants had a mean age of 76.0 years (range: 64.8–88.8), 51.8% were female. The participants reported a median of one chronic co-morbid condition, 12.9% had three or more co-morbid conditions. Three hundred and sixty-one (23.9%) of the 1,509 participants used no medication. The other 1,148 participants used a number of different medications ranging from 1 to 14. The mean number of drugs used by all the participants was 1.89 per participant. Benzodiazepines or benzodiazepine-like drugs were used by 228 (15.1%) participants; 124 (8.2%) used SBs, 116 (7.7%) used LBs. More baseline characteristics are shown in Table 2.

During 1 year of fall registration 468 participants (31%) fell at least once, 174 participants (11.5%) fell two times or more. Fall risk, measured by the time to the first fall was significantly associated with the use of benzodiazepines, hazard ratio (HR) 1.58 [95% confidence interval (CI) 1.10–2.29]. Adjustment for age, gender and co-morbid conditions slightly attenuated this association, HR 1.46 (95% CI: 1.00–2.15) (Table 3). When differentiating between SBs and LBs, only SBs were associated with the risk of falling, HR 1.62 (95% CI: 1.03–2.56). This association was no longer significant.
after adjustment for age, gender and co-morbid conditions (Table 3). Cox-analysis of the use of SBs without zopiclon and zolpidem did not relevantly change the effect-estimate: 1.64 (95% CI: 1.03–2.61).

The number of falls in 1 year of follow-up was associated with the use of both all and SBs. Comparing no falls to one or more falls resulted in odds ratio (OR) 1.28 (95% CI: 1.06–1.54) and OR 1.28 (95% CI: 1.01–1.61) for all and SBs, respectively (Table 4). Adjustment for age, gender and co-morbid conditions rendered the effect-estimates non-significant. The use of LBs was not associated with the number of falls neither without nor with adjustment.

Study 2

A total number of 564 persons participated in the study. Their mean age was 79.0 years (range 65–97), 402 were women (71.3%). The participants reported a median of one chronic co-morbid condition, 9.3% had three or more co-morbid conditions.

The participants used a mean of 5.5 drugs [range 0–21, standard deviation 3.5].

Benzodiazepines or benzodiazepine-like drugs were used by 131 (23.2%) participants. Benzodiazepines with a short elimination half-life were used by 82 (14.5%) and 55 (9.8%) used benzodiazepines with a long elimination half-life. The mean diazepam dose equivalent of the short-acting benzodiazepine users was 3.92 mg/day, versus a mean of 8.18 mg/day for long-acting benzodiazepine users. In 1 year of fall registration, 249 participants (44.1%) fell at least once, 130 participants (23.0%) fell two times or more.

The use of all benzodiazepines and benzodiazepine-like drugs was associated with fall risk, as measured by the time to the first fall, adjusted for gender, age, fall risk intervention and co-morbidity: HR 1.37 (95% CI: 1.03–1.84). The use of SBs with the same additional adjustments was also significantly associated with the time to the first fall: HR 1.56 (95% CI: 1.13–2.16). Cox-analysis of the use of SBs without zopiclon and zolpidem did not relevantly change the effect-estimate: 1.95 (95% CI: 1.39–2.72). No significant association with the use of LBs could be demonstrated (Table 3).

The use of both all and SBs was significantly associated with suffering one or more fall: OR 1.26 (95% CI: 1.03–1.53) and OR 1.37 (95% CI: 1.10–1.70), respectively. This association remained significant for short-acting, but not for all benzodiazepines after adjustment for age, gender, co-morbid conditions and fall intervention. When comparing 0 or 1 fall with 2 or more falls this association was only significant for SBs, OR 1.49 [95% CI: 1.04–2.14], with similar results after adjustment for age, gender, co-morbid conditions and fall intervention. No significant associations were found between the use of LBs and the number of falls (Table 4). The diazepam dose equivalent of the benzodiazepines used was not associated with time to the first fall (P > 0.25) nor with the number of falls (P > 0.5 for a weekly diazepam dose equivalent of ≥35 mg).

Discussion

Contrary to our hypothesis both studies show that the use of benzodiazepines and benzodiazepine-like drugs with a short elimination half-life is associated with increased fall risk in old

Table 2. Characteristics of participants with and without benzodiazepine use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1,281</td>
<td>433</td>
</tr>
<tr>
<td>Age (mean in years)</td>
<td>76.0</td>
<td>78.9</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>51.8</td>
<td>67.0</td>
</tr>
<tr>
<td>Number of chronic diseases (mean)</td>
<td>1.19</td>
<td>1.08</td>
</tr>
<tr>
<td>Number of generic drugs</td>
<td>1.40</td>
<td>1.41</td>
</tr>
<tr>
<td>Neuroleptic use (%)</td>
<td>13 (1.1)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Antidepressant use (%)</td>
<td>25 (2.0)</td>
<td>20 (4.6)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
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<tbody>
<tr>
<td>Neurorhepatic use (%)</td>
<td>13 (1.1)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Number of generic drugs</td>
<td>1.40</td>
<td>1.41</td>
</tr>
<tr>
<td>Number of chronic diseases (mean)</td>
<td>1.19</td>
<td>1.46</td>
</tr>
<tr>
<td>Number of chronic diseases (mean)</td>
<td>1.82</td>
<td>1.08</td>
</tr>
<tr>
<td>Number of chronic diseases (mean)</td>
<td>1.67</td>
<td>0.72</td>
</tr>
<tr>
<td>Number of chronic diseases (mean)</td>
<td>1.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Number of chronic diseases (mean)</td>
<td>1.6</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Table 3. Associations between benzodiazepines with short and long elimination half-life and the time to first fall

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>All benzo-</td>
<td>1.58 (1.10–2.29)</td>
<td>1.41 (1.06–1.86)</td>
</tr>
<tr>
<td>diazepines</td>
<td>1.62 (1.03–2.56)</td>
<td>1.64 (1.19–2.26)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>1.40 (0.85–2.31)</td>
<td>1.08 (0.72–1.62)</td>
</tr>
</tbody>
</table>

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aAdjustment for age, gender, number of chronic diseases (and intervention in Study 2).

bHR, hazard ratio, 95% CI, 95% confidence interval.

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The study and analysis were conducted with the following considerations:

- The use of benzodiazepines and benzodiazepine-like drugs was associated with fall risk, as measured by the time to the first fall, adjusted for gender, age, fall risk intervention and co-morbidity: HR 1.37 (95% CI: 1.03–1.84).
- The use of SBs with the same additional adjustments was also significantly associated with the time to the first fall: HR 1.56 (95% CI: 1.13–2.16).
- Cox-analysis of the use of SBs without zopiclon and zolpidem did not relevantly change the effect-estimate: 1.95 (95% CI: 1.39–2.72).
- No significant association with the use of LBs could be demonstrated (Table 3).
- The use of both all and SBs was significantly associated with suffering one or more fall: OR 1.26 (95% CI: 1.03–1.53) and OR 1.37 (95% CI: 1.10–1.70), respectively. This association remained significant for short-acting, but not for all benzodiazepines after adjustment for age, gender, co-morbid conditions and fall intervention. When comparing 0 or 1 fall with 2 or more falls this association was only significant for SBs, OR 1.49 [95% CI: 1.04–2.14], with similar results after adjustment for age, gender, co-morbid conditions and fall intervention. No significant associations were found between the use of LBs and the number of falls (Table 4). The diazepam dose equivalent of the benzodiazepines used was not associated with time to the first fall (P > 0.25) nor with the number of falls (P > 0.5 for a weekly diazepam dose equivalent of ≥35 mg).

Discussion

Contrary to our hypothesis both studies show that the use of benzodiazepines and benzodiazepine-like drugs with a short elimination half-life is associated with increased fall risk in old

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than the elimination half-life [25]. The higher average diazepam dose was a more important fall and fracture risk factor than the dose equivalent was not found. This contradicts previous studies. In the second study, we were able to reliably compute the diazepam dose equivalent in the long-acting benzodiazepine users, whereas the fall risk increasing properties of SBs use is the not mentioned [11]. The fact that the STOPP criteria, LBs are identified as potentially inappropriate prescriptions, whereas the fall risk increasing properties of SBs use is the not mentioned [11]. The fact that the STOPP criteria do not describe SBs as potentially inappropriate, possibly has a fall risk increasing effect in the older European population. Our findings illustrate the need to intensify the efforts to discourage and discontinue benzodiazepine use.

Explicit criteria aimed at prevention of adverse drug events are quickly gaining importance in clinical practice. Especially the STOPP/START criteria have been researched and implemented in many European countries and generally the medication that is described as inappropriate has been shown to be associated with unfavourable outcomes [26]. In the STOPP criteria, LBs are classified as potentially inappropriate prescriptions, whereas the fall risk increasing properties of SBs use is the not mentioned [11]. The fact that the STOPP criteria do not describe SBs as potentially inappropriate, possibly has a fall risk increasing effect in the older European population. Our findings illustrate the need to regularly revise and update these criteria.

A possible explanation for our findings is the inability of old persons to adapt to the sedative and muscle relaxant effects of agents that do not exercise their effect continuously. These intermittent effects may be more hazardous than an ongoing drug effect that forces users to adapt their behaviour and lifestyle during the period of drug use. The fact that SBs are often prescribed to treat sleep disorders may have led to confounding by indication. However, the proportion of users of benzodiazepines with the primary indication sleep disorder was the same in both the short and long elimination half-life groups of Study 2. This renders confounding by indication less probable.

Another explanation could be that previous studies analysing the effects of SBs and LBs on fall risk used an elimination half-life cut-off of 24 h to define SBs and LBs, respectively [12, 13]. It is probable that the fall risk increasing effect of benzodiazepines with an elimination half-life of ≤10 h went unnoticed because of the clustering with benzodiazepines with a longer elimination half-life.

The strength of these studies lies in the prospective measurement of falls using a fall calendar. This method has a lower rate of underreporting of falls than retrospective collection of fall data [27]. The inclusion of older persons after a fall in Study 2 was aimed at selecting participants with a high fall risk. Thus, we were able to test our hypothesis in both a low to intermediate and a high risk population. This enabled us to determine that the association of the use of SBs with fall risk is more pronounced in a high-risk population.

Although we adjusted our analyses for the intervention, the inclusion of 106 high-risk intervention participants in Study 2 may have influenced the results of this observational parallel study [28]. However, the intervention study was ineffective in its aim to reduce fall risk, which was confirmed by performance of our statistical analysis excluding the intervention participants, resulting in comparable outcomes with a similar level of significance (data not shown).

A limitation of our study is that we were not able to obtain reliable information on the duration of benzodiazepine use, recent dose changes nor on discontinuation or initiation of medication during the course of the study. This may have had an influence on the outcomes. However, this influence was probably not limited to either SBs or LBs thus making a relevant influence on the outcomes of these studies improbable.

Although we adjusted the analyses for relevant confounders like age and co-morbidity, we cannot completely rule out confounding by indication. It is possible that some of the persons with the highest fall risk preferentially were prescribed SBs.

The results of our studies should form a further incentive to intensify the efforts to discourage and discontinue benzodiazepine use in order to reduce fall risk and other adverse

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### Table 4. The associations between benzodiazepines with short and long elimination half-life and the number of falls

<table>
<thead>
<tr>
<th></th>
<th>Short-acting benzodiazepines OR (95% CI)</th>
<th>Long-acting benzodiazepines OR (95% CI)</th>
<th>All benzodiazepines OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 versus ≥1 fall</td>
<td>1.28 (1.01–1.61)</td>
<td>1.17 (0.92–1.48)</td>
<td>1.31 (1.09–1.57)</td>
</tr>
<tr>
<td>0 versus ≥1 fallb</td>
<td>1.17 (0.92–1.48)</td>
<td>1.12 (0.87–1.44)</td>
<td>1.17 (0.96–1.42)</td>
</tr>
<tr>
<td>0–1 versus ≥2 falls</td>
<td>1.53 (1.01–2.33)</td>
<td>1.31 (0.83–2.09)</td>
<td>1.48 (1.06–2.08)</td>
</tr>
<tr>
<td>0–1 versus ≥2 fallsb</td>
<td>1.43 (0.93–2.19)</td>
<td>1.24 (0.77–1.98)</td>
<td>1.40 (0.98–1.99)</td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 versus ≥1 fall</td>
<td>1.37 (1.10–1.70)</td>
<td>1.10 (0.82–1.48)</td>
<td>1.26 (1.03–1.53)</td>
</tr>
<tr>
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<td>1.37 (1.06–1.63)</td>
<td>1.04 (0.77–1.38)</td>
<td>1.19 (0.97–1.45)</td>
</tr>
<tr>
<td>0–1 versus ≥2 falls</td>
<td>1.49 (1.04–2.14)</td>
<td>0.88 (0.51–1.53)</td>
<td>1.25 (0.89–1.75)</td>
</tr>
<tr>
<td>0–1 versus ≥2 fallsb</td>
<td>1.42 (0.99–2.03)</td>
<td>0.88 (0.51–1.52)</td>
<td>1.21 (0.87–1.69)</td>
</tr>
</tbody>
</table>

*a Odds ratio (95% confidence interval).

*b Adjusted for age, sex, chronic diseases (and intervention in Study 2).
Short-acting benzodiazepine use is associated with an increased fall risk and also because of the association of benzodiazepine use with cognitive decline [29]. In persons whose independence is primarily threatened by gait instability and fall risk, it seems feasible to prioritise the effectiveness of discontinuation of benzodiazepines on decreasing fall risk in older persons.

Further research should be directed at determining the effectiveness of discontinuation of benzodiazepines on decreasing fall risk in older persons.

Key points

- The STOPP criteria advise against the use of long-acting benzodiazepines.
- Short-acting benzodiazepine use is associated with an increased fall risk in older persons.
- The use of both short-acting and long-acting benzodiazepines by old persons should be discouraged.

Conflicts of interest

None declared.

Funding

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References

Continuing cancer screening later in life: attitudes and intentions among older adults in England

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Abstract

Background: the rise in life expectancy, together with age-related increase in the incidence of most cancers, has led to mounting interest in cancer screening in older people. In England, routine invitations stop and an ‘opt-in’ (individual request) process is available from ages 71 to 76 years for breast and colorectal screening respectively. Little is known about public attitudes towards age-stoppage policy.

Objective: this study examined public attitudes to current stoppage policy, information preferences and intentions to request screening beyond the age of routine invitations.

Sample: participants (n = 927; age 60–74 years) were recruited as part of a TNS Research International survey and took part in home-based, computer-assisted interviews.

Methods: measures included: (i) attitudes towards current stoppage policy, (ii) preference for communications about screening after the end of the routine invitation period and (iii) intention to opt-in.

Results: the majority of respondents (78%) did not agree with age-based stoppage policies. Most (83%) wanted a strong recommendation to opt-in after this age, although the number who thought they would follow such a recommendation was much lower (27%). A majority of participants (54%) thought information on screening at older ages should come from their general practitioner (GP).

Conclusion: this survey indicates that older people in England wish to continue to be actively invited for cancer screening, although only a minority think that they would ultimately take up the offer. Primary care may play a role in negotiating a shared decision that is based on individual circumstances.

Keywords: cancer screening stoppage, opt-in policy, older age, older people