



## Primary Care Physicians' Use of Antipsychotics for the Treatment of Behavioural and Psychological Symptoms of Dementia in Japan

TOSHIKI TAKAYAMA\*, NOBUTO SHIBATA\*, TOHRU OHNUMA\*, KOICHI MIYAKAWA\*,  
YOSHIHIDE TAKESHITA\*, AYAKO SUZUKI\*, MOTO NISHIGUCHI\*, HEII ARAI\*

\*Departments of Psychiatry, Juntendo University Faculty of Medicine, Tokyo, Japan

**Objective:** We aimed to investigate how primary care physicians (PCPs) in Japan use antipsychotics for treating the behavioural and psychological symptoms of dementia (BPSD).

**Materials and Methods:** A nationwide cross-sectional online survey was conducted of PCPs who annually treated patients aged over 65 years with dementia. Responses from 509 PCPs were analysed by binominal logistic regression analysis.

**Results:** Approximately one-third of the PCPs had treated excitatory BPSD (delusion, hallucination, agitation and violence), with half of them prescribing antipsychotics for this. Some PCPs still prescribed antipsychotics for non-excitatory BPSD, such as wandering. More than half of the PCPs had opportunities to learn about the appropriate use of antipsychotics and understood the increased mortality risk in elderly people with dementia. Referring to the Japanese Government's BPSD guideline for PCPs was negatively associated with antipsychotic dosage (odds ratio = 0.491, 95% confidence intervals 0.32-0.75, p-value = 0.001) and positively associated with a greater awareness of increased mortality with antipsychotics (odds ratio = 2.149, 95% confidence intervals 1.41-3.27, p-value = 0.0004).

**Conclusion:** PCPs continue to prescribe antipsychotics for excitatory BPSD in clinical practice despite official information about mortality risks. Educational material about the appropriate use of the antipsychotics should include specific mention of the risks of using antipsychotics for dementia.

**Key words:** antipsychotics, dementia, primary care physician

### Introduction

It is estimated that 44 million people worldwide suffer from dementia, including Alzheimer's disease, vascular dementia, Parkinson's disease dementia, frontotemporal dementia and Lewy Body dementia, and this number continues to increase<sup>1)</sup>. Japan has one of the highest life expectancies in the world, with elderly people with dementia comprising an increasing proportion of the total population<sup>2)</sup>. In 2015, Japan's Ministry of Health, Labour and Welfare (MHLW) published its Comprehensive Strategy to Accelerate Dementia Measures (known as 'the New Orange Plan') to promote

dementia measures in a holistic way<sup>3)</sup>. This includes establishing specialised facilities, such as dementia-related medical centres, in each local community. However, Japan has only a limited number of experts who can treat patients with dementia; they mainly work in psychiatry, neurology and neurosurgery. Primary care physicians (PCPs) are the doctors who offer general medical care in local communities separate from their specialty departments, such as internal medicine or surgery. PCPs often have opportunities to treat elderly people with dementia before they visit dementia care experts. If a PCP find it difficult to look after a patient with dementia, he or she can refer the patient to a

Corresponding author: Toshiki Takayama

Department of Psychiatry, Juntendo University Faculty of Medicine

2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

TEL: +81-3-5802-1071 FAX: +81-3-5802-1071 E-mail: ttakaya@juntendo.ac.jp

[Received Jan. 5, 2018] [Accepted Feb. 8, 2018]

Copyright © 2018 The Juntendo Medical Society. This is an open access article distributed under the terms of Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original source is properly credited.  
doi: 10.14789/jmj.2018.64.JMJ18-OA01

dementia-related medical centre for more specialised treatment. MHLW expects PCPs to have an important role in dementia medical treatment<sup>4)</sup>.

Among the symptoms that require the most care in the provision of dementia medical treatment are the behavioural and psychological symptoms of dementia (BPSD)<sup>5)</sup>. These include depression, delusions and hallucinations, agitation, violence, wandering, sleep disorder and other manifestations<sup>6)</sup>. Some guidelines indicate that physicians should take a psychosocial approach as the first-line treatment for BPSD, with pharmacological treatment as the second-line approach<sup>7)</sup>. However, in a clinical setting, the situation often arises where antipsychotics are prescribed to treat intense symptoms out of necessity<sup>8)</sup>. In particular, antipsychotics are often considered to manage excitatory BPSD (hallucination, delusion, agitation and violence). Recently, there have been reports of increased morbidity and mortality when patients with dementia take antipsychotics<sup>9-11)</sup>. Following a report in 2005 that reviewed antipsychotic use<sup>12)</sup>, the US Food and Drug Administration announced caution about prescribing conventional and atypical antipsychotic medication to elderly people with dementia-related mental disease because of the increased mortality risk<sup>13) 14)</sup>. A Japanese prospective cohort study also reported increased mortality in patients with dementia who had newly received antipsychotic drugs<sup>15)</sup>. In addition, the cost of care is a serious problem in dementia medical treatment, with the total worldwide societal costs of elderly with dementia estimated to be US\$604 billion in 2010, imposing a tremendous economic burden on society<sup>16)</sup>; the inappropriate use of antipsychotics for BPSD may contribute to this burden. It is therefore necessary for PCPs as well as dementia experts to understand the risks of prescribing antipsychotics to people with dementia. The aim of this study, therefore, was to investigate the practice of PCPs in Japan with regard to prescribing antipsychotics to treat BPSD.

### Materials and Methods

We conducted a cross-sectional questionnaire nationwide online survey of Japanese PCPs in 2015. This was administered by M3, Inc. (Tokyo, Japan) on their website (M3.com). The questionnaire excluded doctors working in specialty departments

(psychiatry, psychosomatic medicine, paediatrics, obstetrics, radiology, anaesthesia and the emergency department), who were not considered to be PCPs. The study protocols were carried out under the Ethical Guidelines for Epidemiological Research (17 June 2002, Ministry of Education, Culture, Sports, Science and Technology and MHLW). After a complete description of the current study and the right to withdraw consent to participate, written informed consent was obtained by electronic signature from all respondents according to the principles of the Declaration of Helsinki (64th, 2013).

In the questionnaire (Table-1), we asked about how PCPs used antipsychotic drugs (regardless of subtypes and dosing regimens of antipsychotics) for BPSDs and how aware they were of the risks of using them. From the questionnaire responses, we investigated several conditions: BPSDs that PCPs targeted for treatment, BPSDs that PCPs prescribed antipsychotics for and the voluntary actions taken by PCPs with regard to BPSD care. Unadjusted and binominal logistic regression analyses were performed to identify factors associated with two dichotomous dependent variables: whether or not PCPs prescribed antipsychotics for elderly people with dementia and whether or not PCPs were aware of the MHLW's warning about the increased risk of mortality from the use of antipsychotic drugs by elderly people with dementia. We simultaneously introduced groups of variables into the model. The potential independent predictors were age, department (internal medicine or surgery), total number of elderly people with dementia treated by the PCP, whether the PCP has participated in a dementia workshop for PCPs hosted by MHLW, the academy, or a pharmaceutical company, whether the PCP refers to MHLW's 'BPSD treatment guidelines for PCPs' and whether the PCP is aware of the MHLW's warning of the increased mortality risk of prescribing antipsychotics for elderly people with dementia. So that multicollinearity did not occur, before performing binominal logistic regression analysis, we performed correlation analyses between dependent variable and each covariate, and confirmed that there was not extremely significant correlation. The results are presented as odds ratios (OR) with 95% confidence intervals (95% CI). The statistical analyses were performed with SPSS for Windows,

**Table-1** Questionnaire

1	How many elderly people with dementia do you treat in total now?	( ) persons
Which BPSDs do you target for treatment?		
2	Depression (yes, no)	Delusion (yes, no)
	Agitation (yes, no)	Violence (yes, no)
	Sleep disorder (yes, no)	Hallucination (yes, no)
Which BPSDs do you prescribe antipsychotics for?		
3	Depression	Delusion
	Agitation	Violence
	Sleep disorder	I don't prescribe
4	Have you participated in a dementia workshop for PCPs hosted by MHLW?	( No opportunity to participate )
		( I sometimes participate )
		( I participate frequently )
5	Do you participate in dementia workshops for PCPs hosted by the academy?	( No opportunity to participate )
		( I sometimes participate )
		( I participate frequently )
6	Do you participate in dementia workshops for PCPs hosted by pharmaceutical companies?	( No opportunity to participate )
		( I sometimes participate )
		( I participate frequently )
7	Do you refer to information on the online homepage of MHLW?	( No opportunity )
		( Sometimes )
		( Frequently )
8	Do you refer to the 'BPSD treatment guidelines for PCPs' published by MHLW?	( No opportunity )
		( Sometimes )
		( Frequently )
9	When you prescribe antipsychotics for elderly people with dementia, are you aware of MHLW's warning? †	( No opportunity to conscious )
		( Conscious )

† MHLW warned of the increased risk of mortality from using antipsychotics for elderly people with dementia.

**Table-2** Characteristics of primary care physicians

• Sex (male/female)	474/35
• Age (years, mean ± SD/range)	53.1 ± 8.9/30-90
• Clinical department (Internal Medicine † / Surgery ‡)	348/161
• Total number of elderly people with dementia treated by the PCP (mean ± SD/range)	72.4 ± 100.5/15-700

† Internal Medicine: General Medicine, Cardiology, Neurology, Respiratory, Nephrology, Gastroenterology, Endocrinology, Haematology, Diabetic Medicine, Rehabilitation, Artificial Dialysis, Geriatric Medicine, Clinical Pathology, Rheumatology.

‡ Surgery: General Surgery, Orthopaedics, Cranial Nerve Surgery, Ophthalmology, Urology, Dermatology, Otorhinolaryngology, Plastic Surgery, Gastrointestinal Surgery, Thoracic Surgery, Cardiovascular Surgery.

version 23.0. For all the analyses, a p-value of < 0.05 was regarded as statistically significant.

## Results

There were 509 respondents and we analysed them. Their characteristics of PCPs are shown in Table-2. Of these, 35 (7%) were women. The mean age was 53.1 ± 8.9 years, and 348 of the PCPs

(68%) were engaged in the clinical department of internal medicine. The mean number of elderly people with dementia treated by each PCP was 72.5 ± 100.5.

BPSDs targeted by PCPs for treatment are shown in Figure-1. The most common BPSD was sleep disorder (357; 70.1%). From one-third to half of the PCPs treated excitatory BPSD delusion, 191

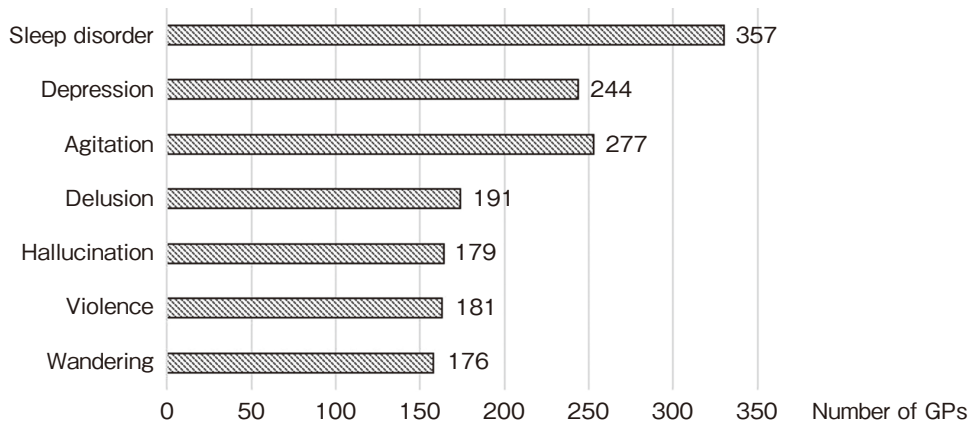


Figure-1 BPSDs targeted by PCPs for treatment

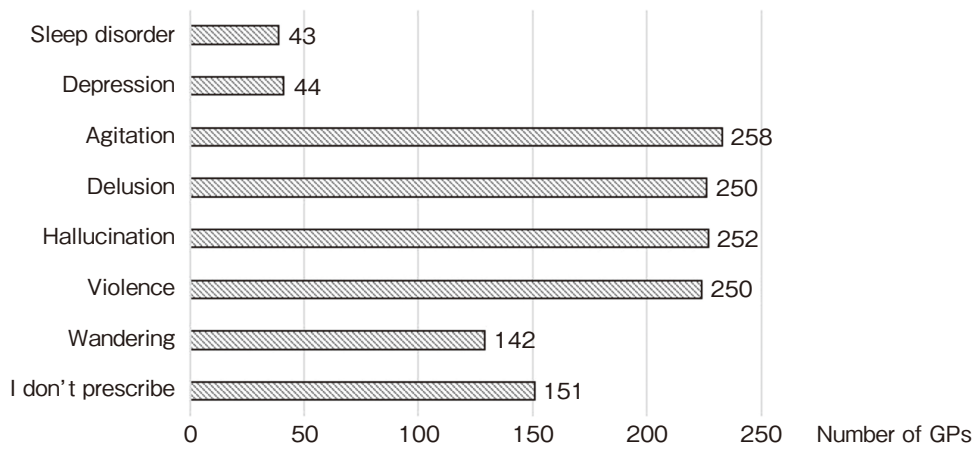


Figure-2 BPSDs for which respondents prescribed antipsychotics

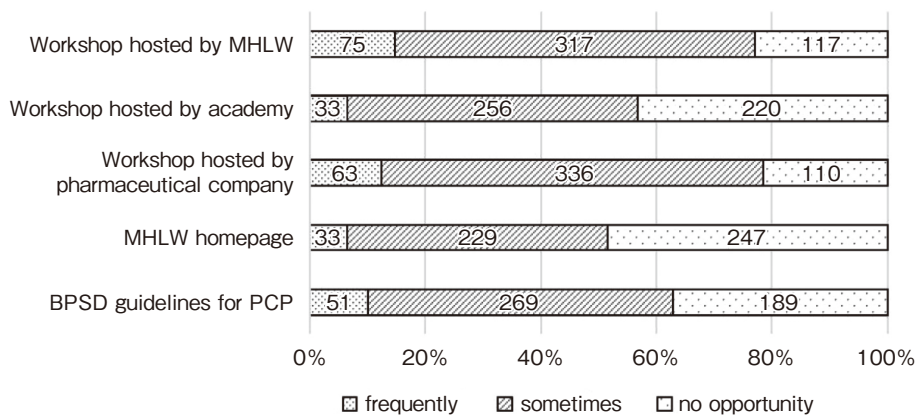


Figure-3 Opportunities through which PCPs learned about BPSD

(37.5%); hallucination, 179 [(35.2%); agitation, 277 (54.4%) and violence, 181 (35.5%)]. BPSDs for which respondents prescribed antipsychotics are shown in Figure-2. Approximately half of the PCPs prescribed antipsychotics for excitatory BPSD [delusion, 250 (49.1%); hallucination, 252 (49.5%); agitation, 258 (50.6%) and violence, 250 (49.1%)].

Approximately one-quarter of the PCPs prescribed antipsychotics for wandering (142, 27.9%). 151 (29.7%) PCPs didn't prescribe antipsychotics for BPSDs.

Figure-3 shows PCPs opportunities to learn about BPSD, and the extent they were aware of the MHLW warning about increased mortality. Half or

**Table-3** Binominal logistic regression analysis of factors potentially associated with prescribing antipsychotics

	OR	95% CI	p-value
Age	1.029	1.01-1.05	0.017 *
Department			
Surgery	1.00 (reference)		
Internal medicine	0.661	0.43-1.02	0.06
Number of people †	0.998	0.99-1.00	0.059
Workshop hosted by MHLW	0.86	0.56-1.33	0.501
Workshop hosted by academy	0.596	0.38-0.93	0.022 *
Workshop hosted by pharmaceutical company	0.72	0.46-1.12	0.146
MHLW homepage	0.899	0.58-1.40	0.638
BPSD guidelines for PCP	0.491	0.32-0.75	0.001 *

OR; odds ratio, CI; confidence interval, MHLW; Japan's Ministry of Health; Labour and Welfare, BPSD; behavioural and psychological symptoms of dementia, PCP; primary care physician.

† Total number of elderly people with dementia treated by PCP. \*  $p < 0.05$

**Table-4** Binominal logistic regression analysis of factors associated with the awareness of risks of antipsychotic use From Questionnaire No.9 (No opportunity to conscious, N=178; Conscious, N=331)

	OR	95% CI	p-value
Age	1.017	0.99-1.04	0.163
Department			
Surgery	1.00 (reference)		
Internal medicine	1.811	1.17-2.81	0.008 *
Number of people †	1.001	0.99-1.01	0.579
Workshop hosted by MHLW	1.369	0.86-2.12	0.158
Workshop hosted by academy	1.481	0.96-2.29	0.078
Workshop hosted by pharmaceutical company	1.252	0.81-1.95	0.317
MHLW homepage	2.204	1.41-3.44	0.0005 *
BPSD guidelines for PCP	2.149	1.41-3.27	0.0004 *

OR; odds ratio, CI; confidence interval, MHLW; Japan's Ministry of Health; Labour and Welfare; BPSD; behavioural and psychological symptoms of dementia, PCP; primary care physician.

† Total number of elderly people with dementia treated by PCP. \*  $p < 0.05$

more of the PCPs had undertaken some kind of learning opportunity about the appropriate use of antipsychotics.

The binominal logistic regression analysis for prescribing antipsychotics revealed a significant negative correlation between workshops hosted by an academy (OR=0.596, 95% CI 0.38-0.93,  $p=0.022$ ) and referring to the MHLW's BPSD guideline for PCPs (OR=0.491, 95% CI 0.32-0.75,  $p=0.001$ ) (Table-3). The binominal logistic regression analysis for PCPs' awareness about the increased mortality risk of using antipsychotics revealed significant positive correlations with being engaged by the internal medicine department (OR=1.811, 95% CI 1.17-2.81,  $p=0.008$ ), referring to MHLW's online homepage (OR=2.204, 95% CI

1.41-3.44,  $p=0.0005$ ) and referring to BPSD guidelines for PCPs (OR=2.149, 95%CI 1.41-3.27,  $p=0.0004$ ) (Table-4).

## Discussion

This study aimed to establish an overview of the practice followed by Japanese PCPs' in the prescription of antipsychotics for BPSD for elderly people with dementia, through the use of an online survey. The results showed that from one-third to half of the PCPs treated excitatory BPSD and approximately half of them prescribed antipsychotics for this. These results were similar to the questionnaire survey for the GP in Australia<sup>17</sup>). From half to two-thirds had taken opportunities to learn about BPSD in one way or another (through workshops,

guidelines, or reference to the MHLW homepage). However, despite the Government's promotion of their strategy about dementia, more than one-quarter of the PCPs still prescribed antipsychotics for wandering (142, 27.9%). Needless to say, when elderly people with dementia are taking antipsychotics, physicians and other health care providers need to pay attention to the risk of the appearance of extrapyramidal symptoms<sup>18) 19)</sup>. For wandering, caregivers should guess the motive why elderly with dementia perform that action and a nonpharmacologic therapy, such as a coordinating environment, should be given priority. It is undesirable to use antipsychotics for the purpose of sedation to suppress wandering; there is a risk of side effects as well<sup>20) 21)</sup>. It seems that the MHLW needs to provide more learning opportunities for PCPs to allow a more appropriate use of antipsychotics.

In England, over half of the care home residents are in residential homes with no nursing staff and general practitioners (who play a similar role to Japanese PCPs) prescribe and are responsible for monitoring medication in care homes<sup>22)</sup>. In 2009, the UK Department of Health reported that the use of antipsychotics for dementia was unacceptably high and recommended a target of a two-thirds reduction over a period of 3 years<sup>23)</sup>. The same year, similar recommendations were incorporated as guidelines in the National Dementia Strategy (NDS) for England launched in February 2009<sup>24)</sup>. However, Szczepura *et al.*<sup>25)</sup> later reported that NDS was not associated with a reduction in prescribing antipsychotics in England or in changes in the types of antipsychotic prescribed in care homes. The authors supposed that the reason why reductions in the prescribing of antipsychotics driven by the NDS were not sustained in care homes was that the length of treatment became excessive because of the lack of regular review by general practitioners. Our statistical analysis indicated that one of the factors that resulted in PCPs becoming more cautious about prescribing antipsychotics for BPSD was referring to MHLW's guidelines. This may be explained by the guidelines describing the risk associated with using antipsychotics; PCPs referred to this and became more careful about using antipsychotics. Another statistically significant factor was age; however, this was considered not to have clinical usefulness because

the odds ratio was extremely close to 1.

The binominal logistic regression analysis suggested that the factors associated with PCPs being aware of the MHLW's warning about the increased mortality risk with using antipsychotics for elderly people with dementia were being engaged by the internal medicine department, referring to MHLW's online homepage and referring to the BPSD guideline for PCPs. The reason why referring to the BPSD guideline raised the awareness of the increased risk of mortality for PCPs was because the guideline had mentioned this risk. Similarly, referring to MHLW's online homepage of MHLW gave access to a link to the guideline, which PCP could then refer to.

Several limitations of the present study should be acknowledged. First, the definition of the PCP may have been indistinct. Results of characteristics of PCPs were based on the respondents' self-assessment, so we were unable to perform enough inspection about years of working as PCP. Whether respondents actually treated elderly with dementia in each local area was unclear. The final sample may be not fully representative of the population of PCPs in Japan. Second, we asked PCPs in the questionnaire whether they had participated in workshops hosted by an academy or pharmaceutical company, but we did not identify which organisations these hosts were. We should have excluded PCPs who had participated in dementia workshops that did not provide information about antipsychotic medication. Finally, the definition of special terms regarding BPSD was unclear. For example, it may be difficult for PCPs to correctly distinguish violence from agitation. Regarding the term, 'wandering', some PCPs might understand that 'wandering' contains 'roaming' that means moving repeatedly in the same space following their pattern, which is often done by patients with frontotemporal dementia. Following this understanding, it might be understandable to prescribe antidepressants. Also, we should have explained especially about agitation, violence and wandering for PCP in detail in the questionnaire.

In conclusion, despite its limitations, this exploratory study provided an overview of the practice of PCPs in prescribing antipsychotics for BPSD and of their behaviour and their opportunities to learn about BPSD. The results suggested that PCPs may

come to use antipsychotics more appropriately by referring MHLW's guidelines that included specific mention about the risks of using antipsychotics for dementia. We hope this study will contribute to an improvement in the quality of primary care for dementia and that it may also result in a reduction in the economic burden.

### Acknowledgements

Financial Disclosures: In 2016, this questionnaire was performed as part of the special study of welfare labour science using the finances of research fund subsidy of the welfare labour science named 'Research about the adequacy of the using psychotropic of the primary care physician for dementia.'

Author Contributions: We asked M3, Inc. to enforce the internet investigation in the internet site called M3.com. The authors would like to thank Enago ([www.enago.jp](http://www.enago.jp)) for the English language review.

### Conflict of interest

The authors have no potential conflicts of interest to disclose.

### References

- 1) Kales HC, Gitlin LN, Lyketsos CG: Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*, 2015; 350: h369.
- 2) Muramatsu N, Akiyama H: Japan: super-aging society preparing for the future. *Gerontologist*, 2011; 51: 425-432.
- 3) Awata S: Medical services for dementia in the Comprehensive Strategy to Accelerate Dementia Measures (New Orange Plan). *Nihon Rinsho*, 2016; 74: 499-504. (in Japanese)
- 4) Ministry of Health, Labour and Welfare: "Comprehensive Strategy to Accelerate Dementia Measures (New Orange Plan)" cited 27 January 2015. Available from: <http://www.mhlw.go.jp/stf/houdou/0000072246.htm>
- 5) Finkel SI, Costa e Silva J, Sartorius N, Cohen G, Miller S: Behavioural and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Int Psychogeriatr*, 1996; 8 Suppl 3: 497-500.
- 6) Carson S, McDonagh MS, Peterson K: A systematic review of the efficacy and safety of atypical antipsychotics in patients with psychological and behavioral symptoms of dementia. *J Am Geriatr Soc*, 2006; 54: 354-361.
- 7) Azermai M, Petrovic M, Elseviers MM, Bourgeois J, Van Bortel LM, Vander Stichele RH: Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms. *Ageing Res Rev*, 2012; 11: 78-86.
- 8) Mann E, Köpke S, Haastert B, Pitkälä K, Meyer G: Psychotropic medication use among nursing home residents in Austria: a cross-sectional study. *BMC Geriatrics*, 2009; 9: 18.
- 9) Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS: Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ*, 2007; 176: 627-632.
- 10) Wang PS, Schneeweiss S, Brookhart MA, *et al*: Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med*, 2005; 353: 2335-2341.
- 11) Gill SS, Bronskill SE, Normand SL, *et al*: Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med*, 2007; 146: 775-786.
- 12) Schneider LS, Dagerman KS, Insel P: Risk of death with atypical antipsychotic drug treatment for dementia meta-analysis of randomized placebo-controlled trials. *JAMA*, 2005; 294: 1934-1943.
- 13) U. S. Food and Drug Administration: FDA public health advisory. Deaths with antipsychotics in elderly patients with behavioral disturbances. Cited 3 November 2005. Available from: <http://www.fda.gov/cder/drug/advisory/antipsychotics.htm>
- 14) Kuehn BM: FDA warns antipsychotic drugs may be risky for elderly. *JAMA*, 2005; 293: 2462.
- 15) Arai H, Nakamura Y, Taguchi M, *et al*: Mortality risk in current and new antipsychotic Alzheimer's disease users: Large scale Japanese study. *Alzheimers Dement*, 2016; 12: 823-830.
- 16) Abbott A: Dementia: A problem for our age. *Nature*, 2011; 475: S2-S4.
- 17) Cousins JM, Bereznicki LR, Cooling NB, Peterson GM: Prescribing of psychotropic medication for nursing home residents with dementia: a general practitioner survey. *Clin Interv Aging*, 2017; 12: 1573-1578.
- 18) Lee PE, Gill SS, Freedman SE, Bronskill SE, Hillmer MP, Rochon PA: Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. *BMJ*, 2004; 329: 75.
- 19) Liperoti R, Pedone C, Corsonello A: Antipsychotics for the treatment of behavioral and psychological symptoms of dementia (BPSD). *Curr Neuropharmacol*, 2008; 6: 117-124.
- 20) Kales HC, Kim HM, Zivin K, *et al*: Risk of mortality among individual antipsychotics in patients with dementia. *Am J Psychiatry*, 2012; 169: 71-79.
- 21) Gitlin LN, Kales HC, Lyketsos CG: Managing behavioral symptoms in dementia using nonpharmacologic approaches: an overview. *JAMA*, 2012; 308: 2020-2029.
- 22) Szczepura A, Nelson S, Wild D: Improving care in residential care homes: a literature review. Cited 29 October 2008. Available from: <http://lx.iriss.org.uk/sites/default/files/resources/improving%20care%20in%20residential.pdf>
- 23) Banerjee S: The use of antipsychotic medication for people with dementia. Time for action. Cited 12 November 2009. Available from: <https://www.rcpsych.ac.uk/pdf/Antipsychotic%20Bannerjee%20Report.pdf>
- 24) Department of Health: Living well with dementia: a national dementia strategy. London: Department of Health. Cited 3 February 2009). Available from: <https://www.gov.uk/government/publications/living-well-with-dementia-a-national-dementia-strategy>
- 25) Szczepura A, Wild D, Khan AJ, *et al*: Antipsychotic prescribing in care homes before and after launch of a national dementia strategy: an observational study in English institutions over a 4-year period. *BMJ Open*, 2016; 6: e009882.