Benzodiazepines and risk of dementia in the elderly

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Abstract

This work deals with the risk of dementia in elderly individuals who have used benzodiazepines. These drugs deserve particular attention because (i) their use appears to be too systematic and most often chronic despite good practice guidelines recommending short durations of use (ii) their deleterious effects on cognition remain underevaluated for the long-term. Most of the studies conducted concluded that there was an increased risk of dementia among benzodiazepine users. In fact, a protopathic bias could, at least in part, have explained these results. Indeed, the prescription of benzodiazepines could have been motivated by the prodromes often observed several years before the clinical diagnosis of a dementia.

With the aim of better controlling for this bias, the BENZODEM project used the resources of the PAQUID cohort (3777 subjects ≥65 years randomly sampled from electoral lists in South-West France, with a 20- year follow-up). This project combined two cohort studies and one case-control. These studies concluded in a risk of dementia increased by 46 to 62% in benzodiazepine users and delayed by 5 to 15 years after treatment initiation. The second part of the programme (BENZODEM2) consisted of a case-control study conducted in a large sample of subjects >65 years registered in the Quebec Health care database (Régie de l'Assurance Maladie du Québec, RAMQ). It was thus possible (1) to validate the previous results by using a different population (the risk was found to be increased by 30 to 80% depending on the patterns of use regarding dose, duration and type of molecule), (2) to identify the patterns of use which appeared to be at risk; excess risk was only apparent for uses of more than three months with a marked dose-effect relationship, and was higher for molecules with a long elimination half-life. Complementary explorations using the PAQUID cohort indicated that the excess risk in exposed was not explained by a differential mortality rate between the groups compared. Other studies suggested that the link found remained independently of the prescription of other psychotropics. Another analysis in the PAQUID cohort showed that, in the absence of dementia, no difference was observed between benzodiazepine users and non-users with regards to the evolution of scores evaluating cognitive functions. These results led to several assumptions about the putative mechanism explaining the relationship found between benzodiazepine use and dementia: (1) benzodiazepines could be early markers of symptoms such as anxiety, depression or insomnia, which are potential prodromes or risk factors for this disease, (2) these drugs could also reduce the ability to use cognitive reserve in order to cope with early lesions of the disease during the preclinical stage, (3) the association found could also result from these two mechanisms.

Key words: benzodiazepines, dementia, Alzheimer's disease, pharmacoepidemiology, longitudinal studies

Résumé

Ce travail porte sur l'étude du risque de démence chez les personnes âgées ayant consommé des benzodiazépines. Ces médicaments méritent une attention particulière du fait de (i) leur utilisation trop systématique et le plus souvent chronique contrairement aux recommandations préconisant des durées d'utilisation courtes (ii) leurs effets délétères sur la cognition demeurant mal évalués à long terme. La plupart des études conduites sur ce sujet ont conclu à une augmentation du risque de démence chez les sujets ayant utilisé des benzodiazépines. Un biais protopathique pouvait cependant, en partie du moins, avoir expliqué ces résultats : la prescription de benzodiazépines pouvait avoir été motivée par des prodromes souvent observés au cours des années précédant le diagnostic de la maladie. Afin de mieux prendre en considération ce biais, le projet BENZODEM a utilisé les ressources de la cohorte PAQUID (3777 sujets ≥ 65 ans tirés au sort sur les listes électorales de Dordogne et Gironde bénéficiant d'un suivi de plus de 20 ans). Ce projet, combinant deux études de cohorte et une étude cas-témoins, a conclu à un risque de démence augmenté de 46 à 62% chez les utilisateurs de benzodiazépines et retardé de 5 à 15 ans par rapport à l'initiation du traitement. La seconde partie du programme (BENZODEM2) a consisté en une étude cas-témoins conduite sur un large échantillon de sujets de plus de 65 ans enregistrés sur la base de données de la Régie de l'Assurance Maladie du Québec (RAMQ). Ce programme a permis (1) de valider les précédents résultats (risque augmenté de 30 à 80% en fonction de la dose, la durée du traitement et la nature des molécules) (2) d'identifier les profils de consommation associés à un excès de risque : consommateurs de plus de 3 mois avec une relation dose-effet marquée et molécules à longue demi-vie d'élimination. Des explorations complémentaires ont permis de conclure que cet excès de risque n'était pas expliqué par une mortalité différentielle entre groupes comparés ni par la prescription d'autres médicaments psychotropes. Une autre étude menée sur PAQUID montrait une absence de différence entre consommateurs et non consommateurs de benzodiazépines vis-à-vis de l'évolution des scores mesurant les fonctions cognitives. Ces résultats ont permis d'émettre des hypothèses concernant le mécanisme de l'association entre utilisation de benzodiazépines et démence: (1) les benzodiazépines pourraient constituer des marqueurs précoces de la maladie ; (2) les benzodiazépines pourraient aussi diminuer les capacités de recours à la réserve cognitive en réponses aux lésions précoces de la maladie au stade préclinique ; (3) il est aussi possible que ces deux explications soient combinées.

Mots clés : benzodiazépines, démence, maladie d'Alzheimer, pharmaco-épidémiologie, études longitudinales

Table of content

REMERCIEMENTS *3*

ABSTRACT *5*

RESUME *6*

LIST OF TABLES *13*

LIST OF FIGURES *16*

LIST OF MAIN ABBREVIATIONS *17*

INTRODUCTION **18**

PART I - PRESENTATION OF THE CONTEXT **22**

1. DEMENTIA 23

1.1. Definition and classification *23*

1.2. Early period and prodromal manifestation of the disease *24*

1.3. Social and economic burden *26*

1.3.1. Incidence and prevalence estimations, projection 26

1.3.2. Evolution of the disease 27

1.3.2.1. Dependency 27

1.3.2.2. Mortality 27

1.3.3. Socio-economic consequences 27

1.4. Risk and preventive factors *28*

1.4.1. Non-modifiable risk factors 28

1.4.2. Lifestyle determinants 29

1.4.3. Cardiovascular risk factors 30

1.4.4. Other medical conditions 31

1.4.5. Environmental risk factors 32

1.5. Interventions *32*

1.6. Risk factors and interventions (summary table) *33*

2. BENZODIAZEPINES 35

2.1. Pharmacology *35*

2.1.1. Mechanism of action and properties 35

2.1.2. Pharmacokinetics 36

2.1.3. Indications 37

2.1.4. Adverse effects 38

2.2. Classification of benzodiazepines *41*

2.3. Data on usage in developed countries *42*

2.3.1. Regulation 42

2.3.2. Prevalence 42

2.3.2.1. Europe 43

2.3.2.2. North America 47

2.3.2.3. Asia-Oceania 48

2.3.3. Patterns and characteristics associated with benzodiazepine use in the elderly 48

2.3.3.1. Characteristics associated with ever use 48

2.3.3.2. Characteristics associated with chronic use 49

3. POTENTIAL RELATIONSHIP BETWEEN BENZODIAZEPINE USE AND DEMENTIA 49

3.1. Reasons for interest *49*

3.2. Possible sources of information for researching a putative association *50*

3.2.1. Pharmacovigilance databases 50

3.2.2. Experimental studies 51

3.2.3. Observational studies 51

4. GENERAL METHODOLOGICAL CONSIDERATIONS FOR EVALUATING THE RELATION BETWEEN BENZODIAZEPINES AND DEMENTIA 53
5. SUMMARY 54

PART II - REVIEW OF STUDIES LOOKING FOR A LINK BETWEEN BENZODIAZEPINE USE AND DEMENTIA 55
1. CONTEXT AND OBJECTIVE 56
1.1. The context in a few questions 56
1.2. Objective 56
2. METHODOLOGY 57
2.1. Search strategy 57
2.2. Summarising the studies 58
2.3. Quality assessment of the studies 58
3. RESULTS 58
3.1. Description of the studies identified 58
3.1.1. Study by Fastbom et al., 1998 59
3.1.2. Study by Lagnaoui et al., 2002 59
3.1.3. Study by Lagnaoui et al., 2009 60
3.1.4. Study by Wu et al., 2009 61
3.1.5. Study by Wu et al., 2011 61
3.1.6. Study by Gallacher et al., 2011 62
3.1.7. Summary of the studies (Table) 63
3.2. Quality assessment of the studies 65
3.2.1. Case-control studies 65
3.2.1.1. Selection of cases and controls 65
3.2.1.2. Comparability 66
3.2.1.3. Ascertainment of exposure 66
3.2.2. Cohort studies 67
3.2.2.1. Selection of exposure groups 67
3.2.2.2. Comparability 68
3.2.2.3. Outcome 68
3.2.2.4. Follow-up duration 68
4. DISCUSSION 69
4.1. Congruence of the results 69
4.1.1. Direction of the results and homogeneity 69
4.1.2. Strength of association and variability 69
4.2. Validity of the results 70
4.3. Opportunities for new studies 72
5. SUMMARY 72

PART III – THE BENZODEM PROGRAMME (PAQUID COHORT) 73
1. CONTEXT AND OBJECTIVE 74
1.1. The context in a few questions 74
1.2. Objective 75
2. STUDY POPULATION: THE PAQUID COHORT 75
2.1. Presentation 75
2.2. Advantages of the PAQUID cohort 76
2.3. Limitations of the PAQUID cohort 76
3. PROSPECTIVE APPROACHES 77
3.1. Presentation 77
3.1.1. Choice of the best adapted design 77
3.1.2. General questions and hypotheses 78
3.2. Main approach 79
3.2.1. Method 79
3.2.1.1. Observation period 79
3.2.1.2. Eligibility criteria 80

3.2.1.3. Exposed groups 80
3.2.1.4. Outcome 81
3.2.1.5. Adjustment 82
3.2.1.6. Statistical analysis 85
3.2.2. Results 86
3.2.2.1. Population selection 86
3.2.2.2. Exposed and non-exposed 87
3.2.2.3. Association between benzodiazepine use and dementia 88
3.2.2.4. Incidence curves 89
3.2.3. Conclusion of the main prospective approach 89
3.3. Second approach: estimation of time-varying exposure 90
3.3.1. Justification 90
3.3.2. Method and results 90
3.3.2.1. Classical method to take into account time-varying exposure 90
3.3.2.2. Advanced methodology estimating the influence of time-varying exposure 92
3.3.3. Conclusion of the second prospective approach 93
4. RETROSPECTIVE APPROACH 94
4.1. Presentation 94
4.2. Method 94
4.2.1. Eligibility 94
4.2.2. Case and control definition 94
4.2.3. Exposure 95
4.2.3.1. Problems of exposure definition 95
4.2.3.2. Exposure definition 97
4.2.4. Adjustment 98
4.2.4.1. Covariates 98
4.2.4.2. Time of covariate measurement 98
4.2.5. Statistical analysis 99
4.3. Results 99
4.3.1. Population selection 99
4.3.2. Comparison of cases and controls 100
4.3.3. Association between benzodiazepine use and dementia 101
4.4. Conclusion 101
5. DISCUSSION 102
5.1. Main conclusions 102
5.2. Strengths of the studies 102
5.3. Limitations of the studies 103
6. COMPLEMENTARY QUESTIONS 104
6.1. Reviewers' questions 104
6.1.1. About reverse causality bias 104
6.1.2. About other confounding 106
6.1.3. About exposure to benzodiazepines 108
6.1.4. About various points 110
6.2. Comments following the publication of our research 111
6.2.1. Influence of elimination of the molecules 111
6.2.2. Influence of mortality rates on the estimates 112
6.2.3. Influence of other psychotropic use on the estimates 112
7. SUMMARY, CONCLUSION AND ADDITIONAL QUESTIONS 113

PART IV – THE BENZODEM2 STUDY (RAMQ DATABASE) 114
1. CONTEXT AND OBJECTIVE 115
1.1. The context in a few questions 115
1.2. Objective 116
1.3. Hypotheses 116
2. STUDY POPULATION: THE RAMQ COHORT 117
2.1. Presentation 117
2.2. Advantages of the RAMQ cohort 117
2.3. Limitations of the RAMQ cohort 118
3. METHODOLOGICAL APPROACH 118

3.1. Design and source population 118
3.1.1. Choice of the design 118
3.1.2. Source population 118
3.2. Case definition and measurement 119
3.2.1. Cases of Alzheimer's disease 119
3.2.2. Minimisation of cases with late report of Alzheimer's diagnosis 120
3.2.3. Cases with long follow-up 120
3.3. Definition of controls 121
3.4. Exposure definition and measurement 121
3.4.1. Measurement in the RAMQ database 121
3.4.2. Observation period 122
3.4.2.1. Decision 122
3.4.2.2. Sensitivity analysis 123
3.4.3. Classification of exposure 123
3.4.3.1. Ever use 123
3.4.3.2. Cumulative dose 123
3.4.3.3. Drug elimination half-life 125
3.4.3.4. Reference group 125
3.4.3.5. Summary of exposure classification 125
3.5. Covariates 125
3.6. Analysis 126
4. MAIN RESULTS AND INTERPRETATION 126
4.1. Population selection 126
4.2. Cases and controls comparison 127
4.3. Association between benzodiazepine use and Alzheimer's disease 127
5. DISCUSSION 129
5.1. Main conclusions 129
5.2. Strengths of the study 129
5.3. Limitations of the study 130
6. COMPLEMENTARY POINTS 131
6.1. Reviewers' questions 131
6.1.1. About the diagnosis of Alzheimer's disease 131
6.1.2. About reverse causality bias 133
6.1.3. About exposure definition 135
6.2. Supplementary research 136
7. SUMMARY, CONCLUSION AND OTHER QUESTIONS 137

PART V - ADDITIONAL TOPICS 138
1. PRESENTATION 139
2. BENZODIAZEPINES AND THE RISK OF DEMENTIA: TAKING MORTALITY INTO ACCOUNT 139
2.1. Competing mortality risk 139
2.1.1. Context and objectives 139
2.1.2. Method 140
2.1.3. Results 140
2.1.4. Discussing competing mortality risk 141
2.2. Benzodiazepines and mortality 142
2.2.1. Context and objective 142
2.2.2. Method 142
2.2.3. Results 142
2.2.3.1. Comparison of exposed and non-exposed 142
2.2.3.2. Survival curves 144
2.2.3.3. Association between exposure and mortality 144
2.2.4. Conclusion about the association between benzodiazepine and mortality 145
2.3. What would happen in the event of differential attrition due to death between comparison groups? 145
2.4. Conclusion about the role mortality 147
3. OTHER PSYCHOTROPIC USE AND DEMENTIA 147

3.1. Was the relation between benzodiazepine use and dementia modified by the use of other psychotropics? *147*
3.1.1. Context and objectives 147
3.1.2. Method 148
3.1.2.1. Analyses conducted within the PAQUID cohort 148
3.1.2.2. Analyses conducted within the RAMQ cohort 148
3.1.3. Results 148
3.1.3.1. PAQUID cohort 148
3.1.3.2. RAMQ cohort 150
3.1.4. Conclusion about the role of other psychotropics 151
3.2. Is there an independent effect of other psychotropics or a synergistic effect with benzodiazepines on the risk of dementia? *151*
3.2.1. Objective 151
3.2.2. Method 151
3.2.2.1. PAQUID cohort 151
3.2.2.2. RAMQ cohort 152
3.2.3. Results 152
3.2.3.1. PAQUID cohort 152
3.2.3.2. RAMQ cohort 154
3.2.4. Conclusion about the independent or synergistic effect of other psychotropics 155
3.3. Discussion about other psychotropic use and dementia *155*
3.3.1. Validity of the relation between benzodiazepine use and dementia considering other psychotropic use 155
3.3.2. Association between other psychotropics and dementia independently of benzodiazepines 156
3.3.3. Synergistic effects of benzodiazepines and other psychotropics on the risk of dementia 156
3.4. Conclusion about other psychotropic use and dementia *157*
4. PATHOGENESIS OF THE RELATIONSHIP 157
4.1. Context and objective *157*
4.2. Hypothesis *157*
4.3. Method *158*
4.3.1. Design, setting 158
4.3.2. Exposure 158
4.3.3. Outcome 158
4.3.4. Statistical analysis 159
4.4. Results *159*
4.5. Discussion about the pathogenesis of the relationship *161*
5. CHARACTERISTICS ASSOCIATED WITH PSYCHOTROPIC USE 161
5.1. Characteristics associated with psychotropic consumption in rural areas: a cross-sectional study using a cohort of retired farmers (AMI) *161*
5.1.1. Context and objective 161
5.1.2. Population, Method 162
5.1.3. Main conclusions 162
5.2. Temporal trends of the characteristics associated with psychotropic use: a study using the PAQUID cohort *165*
5.2.1. Context and objective 165
5.2.2. Population, Method 165
5.2.3. Main conclusions 165

PART VI - GENERAL DISCUSSION 169
1. MAIN RESULTS 170
1.1. BENZODEM and BENZODEM2 *170*
1.2. All studies *172*
2. IS A CAUSAL LINK BETWEEN BENZODIAZEPINE USE AND DEMENTIA LIKELY? 172
3. WHICH POPULATIONS OR USER GROUPS ARE CONCERNED? 174
3.1. Elderly *174*
3.2. Long-term users *174*
3.3. Benzodiazepine-related drugs *175*
4. WHAT ARE THE IMPLICATIONS FOR PUBLIC HEALTH AND CLINICAL PRACTICE? 175

4.1. What would be the consequences in the event of a causal path? 175
4.2. What to do with this knowledge? 175
4.3. What has already been done? 176
4.4. Other perspectives: how to improve monitoring of cognitive side effects of drugs? 176
5. IS THERE OTHER RELEVANT RESEARCH TO BE CONDUCTED ON THE TOPIC? 177
6. SUMMARY 177

GENERAL CONCLUSION 178

FRENCH SUMMARY 181
1. PRESENTATION DU TRAVAIL (INTRODUCTION ET PARTIE I) 182
2. REVUE DE LA LITTERATURE (PARTIE II) 185
3. PROGRAMME D'ETUDES BENZODEM SUR LA COHORTE PAQUID (PARTIE III) 191
4. ETUDE BENZODEM2 SUR UNE BASE DE DONNEES CANADIENNE, LA RAMQ (PARTIE IV) 195
5. ANALYSES COMPLEMENTAIRES (PARTIE V) 198
6. DISCUSSION GENERALE (PARTIE VI) 208
7. CONCLUSION GENERALE 211

REFERENCES 213

ANNEXES 223
ANNEXES 1: PUBLICATIONS 224
ANNEXES 2: COMMUNICATIONS 230
ANNEXES 3: PUBLIC HEALTH COMMUNICATIONS 233
ANNEXES 4: MISCELLANEOUS 249

List of tables

Table 1. Characteristics of dementia subtypes 24

Table 2. Alzheimer's disease cases attributable to potentially modifiable risk factors worldwide and in the USA 33

Table 3. Summary of potential risk factors and intervention for Alzheimer's disease and level of evidence 34

Table 4. Possible characteristics of subjects dependent on a therapeutic dose of benzodiazepines, Ashton Manual, 2002 40

Table 5. General characteristics of main benzodiazepines 41

Table 6. Conditions influencing the choice of the design in observational studies 52

Table 7. Research terms used to identify studies on the relationship between benzodiazepine use and dementia risk 57

Table 8. Inclusion criteria of studies on the link between benzodiazepine use and dementia 58

Table 9. Result of literature search about "benzodiazepine use and dementia" 59

Table 10. Studies having assessed the relationship between benzodiazepine use and dementia 63

Table 11. Quality of the studies evaluated using the Newcastle-Ottawa Scale 68

Table 12. Confidence in the results of studies assessing the relation between benzodiazepine use and dementia 71

Table 13. Number of participants at each follow-up date of the PAQUID study who were available for the BENZODEM programme 75

Table 14. Congruence between depressive symptoms, antidepressant (AD) or benzodiazepine (BZD) use at inclusion (T_0) in the PAQUID study 85

Table 15. Baseline characteristics of participants in the PAQUID programme included in the cohort analysis, according to benzodiazepine use 88

Table 16. Association between new-use of benzodiazepines and incident dementia in the PAQUID study 89

Table 17. Results of a "standard" time-varying Cox proportional hazards model with different definitions of exposure 91

Table 18. Examples of exposure patterns, illustrating the heterogeneity observed during the 20-year follow-up 96

Table 19. Risk of dementia associated with benzodiazepine use in the nested case-control study of 1633 elderly people from PAQUID study 100

Table 20. Risk of dementia associated with benzodiazepine use in the nested case-control study of 1633 elderly people from PAQUID study 101

Table 21. Details of extraction of patients exposed to anticholinesterases (Exposed cohort, EC) and patients not exposed to anticholinesterases (Non-exposed cohort, NEC) 119

Table 22. Non Alzheimer's dementia and corresponding ICD-9 codes 120

Table 23. Elimination half-lives and main indication for benzodiazepines reimbursed by the RAMQ between 2000 and 2009 121

Table 24. Classification of benzodiazepine exposure in BENZODEM2 125

Table 25. Characteristics of subjects with Alzheimer's disease (cases) and controls (variables assessed five to up to 10 years before diagnosis) 128

Table 26. Risk of Alzheimer's disease associated with benzodiazepine use 129

Table 27. Effects of benzodiazepine treatments still active on the date of the dementia diagnosis and discontinued at least one year before (variables assessed 5 to up to 10 years before diagnosis) 133

Table 28. Estimation of the relation between benzodiazepine use and Alzheimer's disease. Results of analysis using cumulative days of exposure compared to the results of analysis using cumulative doses (variables assessed 5 to up to 10 years before diagnosis) 135

Table 29. Estimation of the relation between benzodiazepine use and Alzheimer's disease. Results of analysis considering both cumulative doses and half-lives of the molecules (variables assessed 5 to up to 10 years before diagnosis) 136

Table 30. Comparison between characteristics of users (prevalent or incident) and non-users in the PAQUID cohort at inclusion 143

Table 31. Association between benzodiazepine prevalent use and mortality, PAQUID programme 145

Table 32. Association between benzodiazepine incident use and mortality, PAQUID programme 145

Table 33. Association between benzodiazepine use and death and benzodiazepines and dementia under several simulations of excess mortality in benzodiazepine users and non-users 146

Table 34. Benzodiazepine and other psychotropic use at the BENZODEM study start (T_5) 149

Table 35. Complementary adjustment on other psychotropic use in the main cohort study of BENZODEM (Part III) 150

Table 36. Complementary adjustment on antidepressant use in the case-control study using the RAMQ database (BENZODEM2, Part IV) 150

Table 37. Association between benzodiazepine and other psychotropic ever use in the case-control study using the PAQUID database (BENZODEM, Part III) 153

Table 38. Association between benzodiazepine and other psychotropic use (considering period of use, *i.e.* recent or past initiation) in the case-control study nested in PAQUID programme (BENZODEM, Part III) 154

Table 39. Association between benzodiazepine and antidepressant ever use (observed 5 to 10 years before Alzheimer's disease diagnosis) in the RAMQ case-control study (BENZODEM2, Part IV) 155

Table 40. Baseline characteristics of benzodiazepine new users and non-users 160

Table 41. Effect of benzodiazepine new use on cognitive level and decline according to Mini-Mental State Examination, Isaacs Set Test, and Benton Visual Retention test 160

Table 42. Comparison between psychotropic users and non-users in the AMI cohort at inclusion _____ 163

Table 43. Characteristics associated with psychotropic use in persons 65 years and older included in the AMI cohort_____ 164

Table 44. Prevalence of psychotropic use in two generations of persons aged 75 years and older, included in the PAQUID programme, between 1988-1998 and 2001-2008 _____ 166

Table 45. Comparison of psychotropic users and non-users between 1988 and 1998, among 1882 persons aged 75 years and older, included in the the PAQUID programme_____ 166

Table 46. Comparison of psychotropic users and non-users between 2001 and 2008, among 1212 persons aged 75 years and older, included in the PAQUID programme _____ 166

Table 47. Characteristics associated with psychotropic use between 1988 and 1998 in 1882 persons aged 75 years and older, included in the PAQUID programme_____ 167

Table 48. Characteristics associated with psychotropic use between 2001 and 2008 in 1212 persons aged 75 years and older, included in the PAQUID programme_____ 168

Table 49. Quality of BENZODEM and BENZODEM2 studies assessed by the Newcastle-Ottawa criteria (in comparison with previous works)_____ 170

Table 50. Confidence in the results of studies assessing the relation between benzodiazepine use and dementia _____ 171

List of figures

Figure I. The progressive development of Alzheimer's disease over decades 25

Figure II. Representation of GABA-A receptor 36

Figure III. Follow-up scheme and study design for primary cohort analysis 81

Figure IV. Identification of participants in the PAQUID programme still followed at T_5 and eligible for the main cohort analysis (no dementia and no prevalent benzodiazepine use) 87

Figure V. Dementia-free survival in the PAQUID study in new users of benzodiazepines and non-users at baseline (T_5) 89

Figure VI. Pooled association between new benzodiazepine use at T_5, T_8, T_{10}, T_{13} and T_{15} and the risk of subsequent dementia 93

Figure VII. Nested case-control design within the PAQUID cohort 98

Figure VIII. Identification of participants from the PAQUID study eligible for the nested case-control analysis 100

Figure IX. Dementia-free survival in the PAQUID study in new users of benzodiazepines and non-users at baseline (fifth year). Influence of elimination half-life 112

Figure X. The BENZODEM2 design contrasted with the BENZODEM case-control study 122

Figure XI. Selection of cases in the study on benzodiazepine use and the risk of Alzheimer's disease 127

Figure XII. Comparison between BENZODEM original survival curve (Kaplan Meier) and cumulative incidence curve corrected for mortality as competing risk (Fine and Gray) 141

Figure XIII. Survival curves of benzodiazepine users (prevalent or incident) *versus* non-users 144

List of main abbreviations

ADRDA	Alzheimer's Disease and Related Disorders Association
AIREN	Association Internationale pour la Recherche et l'Enseignement en Neuroscience
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
APA	American Psychiatric Association
ApoE	Apolipoprotein E
APP	Amyloid Precursor protein
BDNF	Brain-Derived Neurotrophic Factor
BVRT	Benton Visual Retention Test
CES-D	Center for Epidemiologic Studies Depression Scale
CIND	Cognitive Impairment No Dementia
CSHA	Canadian Study of Health and Ageing
DDD	Defined daily Dose
DGS	Direction Générale de la Santé
DSM-III-R	Diagnosis and Statistical Manual of Mental disorders, third edition, revised
DSM-IV	Diagnosis and Statistical Manual of Mental disorders, fourth edition
DSM-IV-TR	Diagnosis and Statistical Manual of Mental disorders, fourth edition, revised
DSM-5	Diagnosis and Statistical Manual of Mental disorders, fifth edition
GABA	Gamma-aminobutyric acid
HR	Hazard Ratio
ICD-9	International Classification of Diseases, Ninth Revision
IQR	Inter Quartile Range
IST	Isaacs Set Test
LHID	Longitudinal Health Insurance Database
MBI	Mild Behavioural Impairment
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MSA	Mutualité Sociale Agricole
NHIRD	National Health Insurance Research Database
NICE	National Institute for Health and Care Excellence
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NINDS	National Institute of Neurological Disorders and Stroke
OR	Odds Ratio
PAQUID	Personne Agées QUID?
PDD	Prescribed Daily Dose
PSEN	Presenilin
RAMQ	Régie de l'Assurance Maladie du Québec
RR	Risk Ratio or Relative Risk
SD	Standard Deviation
TBI	Traumatic Brain Injury

INTRODUCTION

Advances made in public health, surgery and drug innovation, especially in the fields of cardiology, cancer and infectious diseases, have contributed to dramatically increasing life expectancy and quality of life in developed countries. For example, life expectancy has increased by about 15 years in the past 50 years and is now estimated to be 78 years between 2010 and 2015 and 83 between 2045 and 2050.[1] The proportion of the population aged 60 years and over in the more developed regions increased from 12% in 1950 to 23% at present and is expected to reach 32% in 2050.[2]

This spectacular increase in life span is also a new challenge for public health with the expected explosion of age related-illnesses, with dementia being perhaps the most disturbing because of its tremendous consequences in terms of seriousness and social costs. The report published in 2012 by the Word Health Organization on dementia[3] noted that: *"the number of people living with dementia worldwide is currently estimated at 35.6 million. This number will double by 2030 and more than triple by 2050."* Although the pharmaceutical industry has made efforts to develop and propose specific preventive or curative medicines, dementia remains currently incurable.

Summarising the current knowledge about the alleged mechanisms for the various types of dementia is outside the scope of our work. However, we will note that the most established risk factors for this disease such as age, gender or genetic profile are, in essence, not alterable and therefore outside the field of prevention strategies. Some lifestyle or environmental factors have been shown to be associated with dementia, but the causal degree of this relationship remains unclear. In the "World Alzheimer Report" published in 2009 by Alzheimer Disease International,[4] the main studies on risk factors for dementia were reviewed and it was pointed out that: "*The evidence for a causal role for cardiovascular risk factors and cardiovascular disease in dementia and Alzheimer's disease is very strong. Unfortunately, attempts to modify cardiovascular risk exposure, by using cholesterol lowering drugs (statins) and antihypertensives, have so far been unsuccessful in reducing the incidence of dementia. This may well have been a case of 'too little, too late'. Hormone replacement therapy had an adverse effect, and a trial of non-steroidal anti-inflammatory drugs had to be stopped because of concerns regarding adverse effects."*

This underlines the importance of focusing on the identification of potential and alterable disease modifiers. In this regard, several observational studies have concluded that there is a possible relationship between benzodiazepine use and dementia, this association being twofold:

(i) First, benzodiazepines could be a risk factor for dementia by reference to their deleterious effects on cognitive functions and particularly on the memory process.[5-9]

(ii) Conversely, these drugs could exert a protective action by an inhibitory effect on glutamate, a neurotransmitter found to be associated with the neurodegenerative process.[10]

In fact, most of the studies published so far have concluded that there is an increased risk of dementia in benzodiazepine users. The degree of causality of this association remains unclear because of limitations due to the numerous and tricky methodological challenges involved when intending to control or even minimise the risk of biased results, a risk that is particularly high in this context. Nevertheless, regarding the high prevalence of both benzodiazepine use and dementia in the elderly, a causal relationship, even partial, would generate a large number of excess cases with dramatic individual and social consequences. It is therefore crucial to clarify the exact nature of this relationship. This would make it possible to develop a scientifically-based communication with prescribers and patients and to introduce specifically adapted health policies for benzodiazepine prescription in order to minimise the possibility of deleterious effects on cognition.

The main objective of our work was to evaluate this relationship between benzodiazepine use and the risk of dementia. For this specific purpose, we have developed original methodological approaches in order to take into account the numerous challenges and pitfalls associated with the study of this association, which include (i) the strength of association is expected to be in the order of magnitude of 2 or lower, (ii) the long latency period of the disease studied makes it impossible to determine its actual onset, (iii) the prodromes of the disease are precisely the reasons for prescribing benzodiazepines, which maximises the risk of reverse causality or protopathic bias.

In the first part of this work, we will describe the context by reviewing and discussing the current knowledge on dementia, benzodiazepines, the reasons for focusing on their putative association, and the methodological challenge represented by the study of this association. The second part will include a brief description and discussion of the existing literature on the topic. In the third part, we will present and discuss the three observational studies we have conducted in the French cohort, PAQUID (two cohort studies and one case-control study), and in the fourth part we will do the same for the case-control study we have conducted by using the reimbursement database of the Quebec Health Insurance (RAMQ). In the fifth part we will develop some specific topics such as benzodiazepines and mortality, association of other psychotropics with dementia, characteristics associated with psychotropic use in a specific population and changes in the characteristics associated with psychotropic use. Part six will consist of a general discussion of the two main questions surrounding benzodiazepines and

dementia: the actual nature of the association, causal or not, and the public health impact this association would have if it were found to be causal.

PART I - Presentation of the context

1. Dementia

1.1. Definition and classification

Dementia is a syndrome linked to brain injury, usually of a chronic and progressive nature. It is characterised by a loss of cognitive abilities in multiple domains, leading to an impairment in normal activities of daily living and resulting in a loss of autonomy. The impairment of cognitive functions is usually accompanied, and occasionally preceded, by a deterioration in emotional control, social behaviour, or motivation.[3] The diagnosis is usually made on the basis of the criteria of the *Diagnostic and Statistical Manual of Mental disorders* (DSM-IV-TR 2000[11] recently modified by DSM-5 2013[12]) published by the American Psychiatric Association (APA) or those established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[13] updated in 2011.[14] The conditions required for a diagnosis of dementia are: (i) a significant impairment of multiple higher cortical functions (at least two) including memory, thinking, orientation, comprehension, computation and learning capacity, language and judgement, (ii) a significant impairment of daily living activities, in the absence of any cause.

Dementia is commonly divided into four subtypes with distinct clinical patterns and possibly pathophysiology (Table 1). These subtypes are in order of frequency: Alzheimer's disease (50-75% of cases of dementia), vascular dementia (20-30%), frontotemporal dementia (5-10%) and dementia with Lewy's Bodies (<5%). Etiological diagnosis should be made by a specialist (neurologist, geriatrician, psychiatrist) according to: the DSM-IV-TR[11]/DSM-5[12] or NINCDS-ADRDA[14] criteria for dementia of the Alzheimer type, the criteria of the National Institute of Neurological Disorders and Stroke and the *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS-AIREN)[15] or DSM-IV-TR criteria for vascular dementia,[11] Mac Keith's criteria (2005) for dementia with Lewy Bodies,[16] and Neary's criteria (1998) for frontotemporal dementia.[17] Classifying individuals into one of these subtypes remains challenging since an indisputable diagnosis may only be made on the basis of a post-mortem examination; moreover, mixed forms are common, particularly Alzheimer's disease with vascular lesions.

Table 1. Characteristics of dementia subtypes
(extracted from the World Alzheimer's Report 2009, *Alzheimer's Disease International*[4])

Dementia subtype	Early, characteristic symptoms	Neuropathology	Proportion of dementia cases
Alzheimer's disease*	Impaired memory, apathy and depression Gradual onset	Cortical amyloid plaques and neurofibrillary tangles	50-75%
Vascular dementia*	Similar to Alzheimer's disease, but memory less affected, and mood fluctuations more prominent Physical frailty Stepwise onset	Cerebrovascular disease Single infarcts in critical regions, or more diffuse multi-infarct disease	20-30%
Dementia with Lewy Bodies	Marked fluctuation in cognitive ability Visual hallucinations Parkinsonism (tremor and rigidity)	Cortical Lewy bodies (alpha-synuclein)	<5%
Frontotemporal dementia	Personality changes Mood changes Disinhibition Language difficulties	No single pathology – damage limited to frontal and temporal lobes	5-10%

*Post mortem studies suggest that many people with dementia have mixed Alzheimer's disease and vascular dementia pathology, and that this "mixed dementia" is underdiagnosed.

1.2. Early period and prodromal manifestation of the disease

The time course of the disease could be seen as a long continuum (Figure I). It is first characterised by a *latent period* (of unknown duration and likely to vary markedly across individuals and according to the type of dementia) during which neuronal dysfunction or cell death are without consequence. The following stage is the *prodromal phase,* defined as the transition between the latent period and a clinically diagnosed dementia. As the term *prodromal* suggests, the worsening of the process leads to a progressive and measurable alteration of cognitive functions and to a higher prevalence of some symptoms, notably neuropsychiatric. The extent of this prodromal phase is debated, 10-12 years seeming to be a minimum for many authors.[18 19] One should note that when the DSM-IV-TR[11] or DSM-5[12] criteria are met to ascertain the diagnosis, the disease is already in an advanced stage. From a public health perspective, identifying diseased individuals during the prodromal phase could optimise the early-care management of the disease and reduce its impact on cognitive functions and quality of life, through actions allowing patients to maintain functional abilities as long as possible. This explains the extensive research conducted on characterising early manifestations of the disease in the last decade.

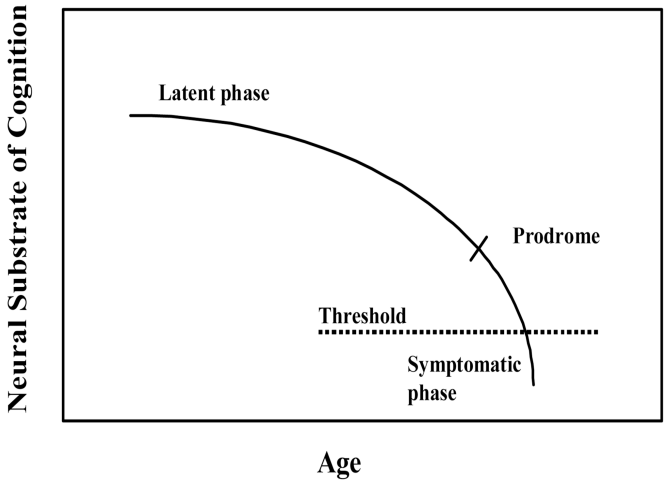


Figure I. The progressive development of Alzheimer's disease over decades (extracted from the article by Welsh-Bohmer *et al.*[20])

Several concepts have successively emerged in the literature to characterise individuals involved in a potential early phase of dementia, for example:

- *Mild Cognitive Impairment (MCI)* is currently the leading concept. The most prominent classification defined by Petersen *et al.* in 1999[21] included elderly subjects with short-term or long-term memory impairment (*i.e.* subjective memory complaint, impaired performance on objective memory tests) with no significant daily functional disability and non-demented status. It was presented as a transitional state between normal ageing and dementia. Petersen *et al.* initially reported a 12% conversion rate from MCI (defined using their own clinical criteria) toward Alzheimer's disease in a sample of patients from a general community clinic. The MCI concept has been criticised as being over-inclusive or imprecise since: (i) its diagnostic criteria were insufficiently standardised,[22] (ii) they were found to perform poorly in predicting the risk of dementia over 3 years when applied to a general population,[23] and (iii) a significant part of subjects diagnosed as MCI do not progress to dementia or revert back to a diagnosis of no cognitive impairment.[24 25] MCI has been further subdivided into the amnestic form (subjects with cognitive impairment relative to memory disorders) and the non-amnestic form (cognitive impairment but without memory disorder). Amnestic MCI would be more predictive of Alzheimer's disease, while the non-amnestic form would mainly be correlated with a greater risk of dementia of other types (*i.e.* Lewy bodies, vascular, frontotemporal).[26] Over a period of years, the MCI criteria have been revised and they were recently updated by Albert *et al.* and the International Working group on Mild Cognitive Impairment.[27]

- The notion of *Cognitive impairment No Dementia (CIND)* was introduced to characterise individuals, aged 65 and over, presenting troubles involving memory and/or other aspects of cognition but not sufficiently severe to meet the criteria for dementia. The definition does not rely on a universally accepted cut-off. These subjects were thought to differ from similarly aged but cognitively normal individuals.[28] CIND was not defined as a prelude to Alzheimer's disease since it also concerns a heterogeneous set including vascular brain disorders and other causes of cognitive impairment.

- The syndrome of *Mild Behavioural Impairment (MBI)* was more recently proposed[29] to characterise individuals: (i) presenting persistent behavioural changes (*e.g.* agitation, anxiety, apathy, depression, delusion, sleep disorders, loss of social skills, perseverant behaviours, loss of insight, dietary changes, impulsivity, irritability) and mild psychiatric symptoms, especially disinhibition, (ii) without serious cognitive complaints, (iii) conserving normal daily living activities, and (iv) not meeting diagnostic criteria for dementia. Taragano *et al.* concluded that MBI would carry a higher risk of conversion to dementia than MCI.[29]

However, much remains to be done in characterising the progression of dementia (*e.g.* duration of the latency period, identification of early markers). Moreover, research into symptoms characterising a "pre-disease condition" is subject to methodological and conceptual limitations. First, the definition of these early states may include individuals who are quite heterogeneous with regards to the risk of future dementia. Second, it could open the door to a "pathologisation", stigmatisation and medicalisation of normal or pseudo-normal ageing.

1.3. Social and economic burden

1.3.1. Incidence and prevalence estimations, projection

In 2010, the World Health Organization estimated the total number of persons presenting with dementia worldwide to be 35.6 million with an annual incidence of 7.7 millions.[3] Prevalence of the disease could double every 20 years leading to 65.7 millions of cases in 2030 and to 115.4 millions in 2050.[3] From 2020, one in four French people over 65 is likely to develop a form of Alzheimer's disease.[30]

Figures for incidence and prevalence of dementia may appear discrepant across countries or studies. This could be due to differences in: (i) definition or criteria used for the diagnosis,

(ii) methods used to measure incidence and prevalence; reliable estimates should ensue from longitudinal surveys of large and representative samples with an active search for cases, (iii) access to medical services or to treatments proposed in early stages of the disease which could affect the probability of an early diagnosis, or (iv) life expectancy itself, which is strongly correlated with the probability of dementia.

1.3.2. Evolution of the disease

1.3.2.1. Dependency

Dementia is one of the major causes of disability in late-life.[3] [4] In everyday life, dementia primarily affects cognitively complex activities (*e.g.* making phone calls, managing his/her budget or orientation capacities) before gradually affecting basic activities (*e.g.* dressing, eating).[31] [32] Dependency progresses irrevocably, becoming total at the end of the process. Disability is observed in the majority of the time course of the disease, in contrasts to other chronic illnesses such as cancer.

1.3.2.2. Mortality

A meta-analysis of studies (mainly including high-income countries) estimated that for people with dementia the risk of mortality was more than double.[33] This is confirmed by a study conducted in European countries.[34] Median survival was estimated to be around 7 years for Alzheimer's disease and 4 years for vascular dementia.[35] The report of median survival is constantly lower for vascular dementia than Alzheimer's disease. In general, women with dementia have a longer survival than men, this difference being even greater in Alzheimer's disease.[36]

1.3.3. Socio-economic consequences

As a result of its high prevalence (0.5% of the world population) and costs associated with patients' health care, dementia has a huge socioeconomic impact worldwide, estimated by the World Health Organization at 604 billion US Dollars in 2010 (about 1% of the World Gross Domestic Product, GDP).[3] These costs, already considerable, are expected to increase even more quickly than the prevalence of the disease and will challenge the sustainability of health care systems. Dementia is also a considerable physical, psychological and economic burden for the relatives, family and caregivers of patients, and has tremendous consequences.

1.4. Risk and preventive factors

Owing to the lack of any effective treatment, identifying alterable risk factors is a major challenge for epidemiologic research on Alzheimer's disease and dementia. Most of the studies conducted on this topic focused on Alzheimer's disease, with research on vascular dementia being concentrated on vascular risk factors. An extensive literature exists on the possible modifying effects of cardiovascular diseases, diet and nutrition, life habits, environmental exposure and medical history, etc. Although Alzheimer's disease mostly affects the elderly, recent research frequently explores the characteristics of individuals at mid-life and even young age periods. Indeed, a factor modifying the probability of onset of a chronic disease in the elderly can have its origin several decades before with a possible cumulative effect.[37] As we shall discuss extensively in this thesis, this could be the case for anxiety and depression. Nevertheless, to date, the pathophysiological mechanism of the disease remains unknown, especially as it is certainly multi-factorial. We will focus on risk factors for dementia with a specific interest in Alzheimer's disease.

1.4.1. Non-modifiable risk factors

Age

It will come as no surprise to learn that the most established risk factor for most forms of dementia is advanced age. Clinical onset of the disease is mostly observed over 65 years, with the prevalence of the disease being roughly doubled every five years after this age.[4]

Gender

Women are at greater risk of Alzheimer's disease, particularly after 80 years. Numerous explanations have been advanced: oestrogen deficiency after menopause, higher life expectancy, socio-cultural habits, and gender-linked genetic traits.[38] [39]

Genetics

Depending upon a gene mapped to chromosome 19, the apolipoprotein E (ApoE) is polymorphic with three major alleles: ApoE2, ApoE3 and ApoE4. The ApoE4 isoform is the largest known genetic risk factor for late and sporadic Alzheimer's disease.[40] Depending on sources, carriers of one or two E4 alleles are said to have respectively between 3 to 6, and 8 to 30 times the risk of developing the disease when compared to subjects of the same age but not carrying this allele.[40] [41] The exact role of ApoE4 in the pathophysiological mechanism of the disease remains unclear. At the histological level, Alzheimer's disease is characterised by build-ups of aggregates of beta-

amyloid peptide. ApoE enhances the proteolytic breakdown of this peptide. The ApoE4 is less effective than other isoforms, which would put carriers of this isoform at risk.[42] Things are certainly more complex since the ApoE4 isoform is not found in all subjects presenting an Alzheimer's disease and not all ApoE4 carriers develop the disease. Several other genes have been identified as susceptibility factors possibly increasing the risk of late-onset Alzheimer's disease.[38]

Inherited forms of Alzheimer's disease transmitted in an autosomal dominant way probably account for less than 5% of the cases of the disease and generally occur in midlife (before 65 years and often around 45 years). In half of these cases, mutations affecting three genes have been identified: one coding for a precursor of the amyloid peptide (Amyloid Precursor Protein or APP) and two others for presenilins 1 and 2 (multipass transmembrane proteins, PSEN1 and PSEN2) implicated in the catabolism of APP.[43]

1.4.2. Lifestyle determinants

Educational level, occupation, social network and activities

Higher educational level and increased occupational attainment have been found to be associated with a lower risk of dementia or a delayed onset of cognitive troubles.[44] [45] More than the absolute number of schooling years, the level achieved appears to be determinant.[46] [47] Education level is also a marker of socio-economic status; however, the association with dementia seems to remains independent of income or socio-professional class.[48]

People living alone or who are single have been found to have almost double the risk of developing dementia compared to those living in couples.[49] A low social status was also found to be associated with a 60% increased risk.[50] Moreover, permanent brain stimulation through social interactions and leisure activities (such as gardening, travelling, handiwork, knitting, conferences, etc.) decreases the chances of presenting Alzheimer's disease.

Having a high educational level, a stimulating professional activity, maintaining an active and social lifestyle in old age could delay the development of cognitive alterations and/or reduce their severity. This protective effect is likely to be linked with brain plasticity, reflecting the permanent adaptability of the brain to life-style conditions or lesions. This could rely on the development of a dense neural network (*i.e.* cognitive reserve) allowing the mobilisation of supplementary neural networks to cope with early lesions of the disease.[51] In that sense, promoting the development of cognitive reserve through brain stimulation appears to be one of the few protective actions known to delay the onset of dementia.

Nutrition and physical activities

Several studies conducted in the last decades have shown that a Mediterranean-style diet is associated with a decrease in both cardiovascular diseases and global mortality.[52] [53] In its classical form, this diet combines a high proportion of vegetables, fruits, cereals, non-unsaturated fats (*e.g.* olive oil) and a moderate and regular consumption of wine, with a preference given to fish over dairy products and meat. Independently of vascular dementia, such a diet was also found to have an inconstant and relatively moderate protective effect against cognitive disorders and possibly Alzheimer's disease.[54] [55] Other studies pointed to the advantages of a regular intake of antioxidants (*e.g.* alphatocopherol, selenium or carotenoids). To date, the body of evidence is not sufficient to justify massive information campaigns on that practice.[56]

The majority of studies conducted on the topic have suggested that a regular physical activity is associated with a lower risk of Alzheimer's disease. However, because of the colinearity expected to exist between this practice, healthy food habits and educational level, no clear-cut conclusion can be drawn.

Alcohol and smoking

A moderate and regular consumption of alcohol or wine has been found to be associated with a lower risk of Alzheimer's disease. Even if this finding is more than debatable, several explanations have been proposed:[57] (i) this type of consumption (regular and moderate) is just a marker for populations known to be at lower risk (high educational level, healthy food habits, etc.), (ii) stimulation of hippocampic cholinergic neural networks, (iii) preventive action on cardiovascular risk factors, and (iv) antioxidant effects of polyphenols present in red wine.

A meta-analysis concluded that there was an increased risk of Alzheimer's disease in current smokers compared to never or former smokers (RR 1.79, 95%CI 1.43 to 2.23 and 1.70 (1.25 to 2.31), respectively).[58] The excess risk was higher for Alzheimer's than for other types of dementia. No association was found for former smokers when compared to never smokers (RR 1.01 (0.83 to 1.23)). Nevertheless, the effect of cumulative durations of exposure or non-exposure was not assessed; nor was the delay before a former user returns to the baseline risk.

1.4.3. Cardiovascular risk factors

Possibly because of some common pathophysiological paths, dementia shares several risk factors with cardiovascular diseases: systemic hypertension, hypercholesterolaemia, diabetes, smoking, alcohol abuse, overweight, etc. Several cardiovascular diseases are also considered as risk factors for dementia: heart failure, coronary diseases, arterial fibrillation, history of stroke,

etc. The period of onset of these conditions seems to play a role. For example, for hypertension, obesity and dyslipidaemia, the risk of dementia was generally found higher when the risk factor was identified in midlife (compared to late life), corresponding to a long exposure. Conversely, a recently identified diabetes would carry the highest risk of dementia. Similarly, dementia was found associated with lower blood pressure, dyslipidaemia and obesity identified within the few preceding years. Treating such cardiovascular risk factors could be considered as a major target for prevention of dementia, even if the chronological sequence appears to be critical.[59]

1.4.4. Other medical conditions

Depression and anxiety

Depression is indisputably associated with an increased risk of dementia. However, the exact nature of this association is controversial. Indeed, depression could be a risk factor for dementia, as some studies showed that recurrent depression episodes in midlife are associated with a higher probability of presenting dementia several decades later.[60] [61] The same has been shown for severe and long-lasting anxiety.[62] The association could also be explained by the fact that the prevalence of depressive disorders increases in the early and infra-clinical phase of dementia and is considered by many as a prodrome of the disease.[63] [64] The two hypotheses are not mutually exclusive even if a depressive episode occurring a few years before the diagnosis of a dementia should be considered as belonging to its prodromal phase, particularly if it is not responding to antidepressants.[65]

Traumatic brain injuries (TBI)

Several studies have shown a significant impact of TBI on the risk of Alzheimer's disease. Differences across studies seem to be due, at least in part, to heterogeneity in the severity and seriousness of the head trauma and in the delay observed between the trauma and the dementia.[66] A recent cohort study concluded that moderate to severe traumatic brain injuries increased the risk of dementia in individuals aged 55 years and over (55-64: HR 1.72 (1.40 to 2.10); 65-74: HR 1.46 (1.30 to 1.64)) even for mild forms, at least for the upper classes of age (55-64: HR 1.11 (0.80 to 1.53); 65-74: HR 1.25 (1.04 to 1.51)).[67] A systematic review of case-control studies concluded that there was an increased risk of Alzheimer's disease in men with a history of TBI, even in early adulthood (OR 2.29 (1.47 to 3.58)), but not in women (OR 0.91 (0.56 to 1.47)).[68]

Sleep apnoea

The link between sleep apnoea and Alzheimer's disease is supported by two-sided arguments: cognitive disorders are more prevalent in subjects suffering from sleep apnoea and a higher rate of sleep apnoea is observed in patients with dementia. Several hypotheses have been put forward, such as cardiovascular and cerebrovascular consequences of sleep apnoea which could contribute to exacerbate the lesions induced by the Alzheimer's disease; or the higher frequency of sleep apnoea in carriers of the ApoE4 isoform.[69]

1.4.5. Environmental risk factors

Various factors have been presented as being associated with an increased risk of dementia: exposure to electromagnetic fields, solvents, or pesticides. Negative studies are more frequent for electromagnetic fields and solvents, while results are more consistent for pesticides. Even if their role has been strongly debated, one can conclude that traces of lead and aluminium ingested in food do not significantly act on the probability of presenting Alzheimer's disease.[70] Even if the findings are not conclusive, the same could be said for mercury (sea pollution and dental amalgams).

In a systematic review of risk factors for Alzheimer's disease and dementia the authors concluded: "*few cohort studies have examined the association between toxic-environmental exposure and risk of Alzheimer's disease. Most case-control studies have important methodological limitations that may bias the results. Among the exposure considered, only pesticide showed a consistent association with Alzheimer's disease*".[66]

1.5. Interventions

Despite intensive research conducted since the early 90's, there is currently no curative treatment for dementia that has met the basic requirements for a treatment of this type, *i.e.* effectiveness (i) observed in a majority of patients, (ii) resulting in a significant improvement in daily activities, (iii) maintained for several years. To date, "specific" treatments are purely symptomatic with inconstant results and are less systematically prescribed. For these reasons, we will not discuss this further. As suggested above, another track is the treatment of symptoms or diseases suspected of being risk factors or worsening conditions for dementia, like systemic hypertension, diabetes, depression or anxiety. In this context, the World Alzheimer report published by the World Health Organization in 2012[3] indicated that: *"Primary prevention measures should focus on targets suggested by current evidence, namely: improving access to education and countering risk factors for vascular disease, including diabetes, midlife hypertension,*

midlife obesity, smoking, and physical inactivity." The number of cases and the preventive fraction related to seven main modifiable risk factors have been evaluated by Barnes *et al.* in 2011.[71] These estimates are given in Table 2.

Table 2. Alzheimer's disease cases attributable to potentially modifiable risk factors worldwide and in the USA (extracted from the article by Barnes *et al.*[71])

	Population prevalence	Relative risk (95% CI)	PAR (confidence range)	Number of cases attributable (thousands; confidence range)
Worldwide				
Diabetes mellitus	6·4%	1·39 (1·17–1·66)	2·4% (1·1–4·1)	826 (365–1374)
Midlife hypertension	8·9%	1·61 (1·16–2·24)	5·1% (1·4–9·9)	1746 (476–3369)
Midlife obesity	3·4%	1·60 (1·34–1·92)	2·0% (1·1–3·0)	678 (387–1028)
Depression	13·2%	1·90 (1·55–2·33)	10·6% (6·8–14·9)	3600 (2295–5063)
Physical inactivity	17·7%	1·82 (1·19–2·78)	12·7% (3·3–24·0)	4297 (1103–8122)
Smoking	27·4%	1·59 (1·15–2·20)	13·9% (3·9–24·7)	4718 (1338–8388)
Low education	40·0%	1·59 (1·35–1·86)	19·1% (12·3–25·6)	6473 (4163–8677)
Combined (maximum)	..	..	50·7%	17 187 028*
USA				
Diabetes mellitus	8·7%	1·39 (1·17–1·66)	3·3% (1·5–5·4)	174 (77–288)
Midlife hypertension	14·3%	1·61 (1·16–2·24)	8·0% (2·2–15·1)	425 (119–798)
Midlife obesity	13·1%	1·60 (1·34–1·92)	7·3% (4·3–10·8)	386 (226–570)
Depression	19·2%	1·90 (1·55–2·33)	14·7% (9·6–20·3)	781 (506–1078)
Physical inactivity	32·5%	1·82 (1·19–2·78)	21·0% (5·8–36·6)	1115 (308–1942)
Smoking	20·6%	1·59 (1·15–2·20)	10·8% (3·0–19·8)	574 (159–1050)
Low education	13·3%	1·59 (1·35–1·86)	7·3% (4·4–10·3)	386 (236–544)
Combined (maximum)	..	..	54·1%	2 866 951*

PAR=population attributable risk. *Absolute number.

1.6. Risk factors and interventions (summary table)

In a recent meta-analysis, Williams *et al.*[66] summarised the risk factors and putative modifiers for Alzheimer's disease. These parameters are listed in Table 3 with their level of evidence.

Table 3. Summary of potential risk factors and intervention for Alzheimer's disease and level of evidence (extracted from the article by Williams *et al.*[66])

Direction of association	Factors	Level of evidence†
Increased risk	- ApoE4 genotype - Conjugated equine oestrogen with methyl progesterone*	Moderate
	- Some non-steroidal anti-inflammatory drugs* - Depressive disorder - Diabetes mellitus - Hyperlipidaemia in mid-life - Traumatic brain injury in males - Pesticide exposure - Never married, less social support - Current tobacco use	Low
Decreased risk	- Mediterranean diet - Folic acid - HMG-CoA reductase inhibitors (statins) - Higher levels of education - Light to moderate alcohol intake - Cognitively engaging activities - Physical activity, particularly high levels	Low
No association	- Ginkgo biloba*	High
	- Vitamin E* - Cholinesterase inhibitors*	Moderate
	- Anti-hypertensive medication* - Conjugated equine oestrogen - Omega-3 fatty acids* - Vitamin B12, C, beta-carotene - Homocysteine - Hypertension - Obesity - Metabolic syndrome - Early childhood factors - Occupational level - Lead	Low
Inadequate evidence to assess association	- Saturated fat intake - Fruit and vegetable intake - Trace metals - High caloric intake - Memantine - Sleep apnoea - Anxiety disorders - Resiliency - Non-cognitive, non-physical leisure activities - Agent Orange, Gulf War Syndrome - Solvents, aluminium - Genetic factors other than ApoE	(Not applicable)

ApoE=apolipoprotein E gene. ApoE4=epsilon 4 allele of the apolipoprotein E gene.
HMG-CoA=3 hydroxy-3-methylglutaryl-coenzyme A.
*Data from observational studies and randomised controlled trials.
†GRADE criteria.[72]

2. Benzodiazepines

Benzodiazepines are a homogenous class of chemical compounds formed by a diazepine ring fused with a benzene ring. The first molecule (Chlordiazepoxide, Librium®) was discovered by Sternbach and Reeder, researchers at Hoffmann-Laroche (Basel, Switzerland) and marketed in 1960. Numerous other molecules were developed in the sixties and seventies, first as anxiolytic drugs with Diazepam (best known as Valium®) marketed in 1963, and then as hypnotics with Flurazepam. The good safety profile of benzodiazepines rapidly made barbiturates obsolete (their much more toxic and addictive profile are the reason for their quite marginal use today).

2.1. Pharmacology

2.1.1. Mechanism of action and properties

GABA or gamma-aminobutyric acid is the chief inhibitory neurotransmitter in the central nervous system. Its pharmacological effects are achieved through three receptors: GABA-A, GABA-B and GABA-C. The ionotropic GABA-A receptor is widely distributed in the nervous system (central and peripheral) and even found in non-neuronal tissues. It is a transmembrane receptor that consists of five subunits (α, β, γ, δ and ε) arranged around a central pore permeable to chloride ions. Stimulation of the receptor changes conformation within the membrane, which opens the pore and allows chloride anions to pass. This results in a hyperpolarisation of the membrane, making it more difficult for excitatory neurotransmitters to generate an action potential, which explains the inhibitory effect of GABA-agonists. Benzodiazepines bind with the subunit α of the GABA-A receptor, increasing the affinity of the subunit β for GABA (positive allosteric effect). The increased chloride entrance results in an inhibition of neuronal activity (Figure II). Therefore, benzodiazepines potentialise GABA effects.

Basically, all benzodiazepines share common pharmacologic properties: anxiolytic, hypnotic, sedative anticonvulsant, muscle relaxant, and amnesic. As a consequence, they have potentially the same therapeutic indications and side effects. Nevertheless, the pharmacology of this family is rather complex and marked differences across products have been noted, although not always explained. These differences could ensue from: (i) pharmacodynamic differences. For example, a molecule can express a more marked sedative effect or a specific property like an euphoriant effect. This probably results from differences in affinity for the various subtypes of alpha-GABA-A receptors. (ii) However, differences in pharmacokinetic properties explain most of the differences across molecules and their preferential indications. For example, for a hypnotic, a

molecule with a rapid absorption after oral ingestion and a short to intermediate duration of effect is preferred.

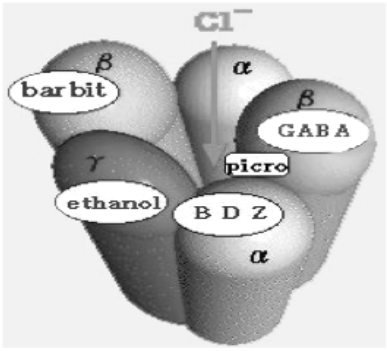


Figure II. Representation of GABA-A receptor

2.1.2. Pharmacokinetics

After oral administration, intestinal absorption of benzodiazepines is good and generally rapid, despite marked variations across products. In the blood flow, they express a high affinity for the plasmatic protein binding sites, as shown by the value of the bind fraction (around 85%) remaining stable whatever their blood concentration. Like all products acting on the central nervous system, benzodiazepines are liposoluble and consequently widely distributed into tissues and easily pass through the blood brain barrier. Almost all the molecules are metabolised by the liver by demethylation or hydroxylation, leading to active or inactive metabolites (some of these active metabolites have a longer elimination half-life than the original molecule), and/or by conjugation leading to inactive compounds. The persistence of the molecule and/or of its active metabolites in blood and brain tissues can be extremely long after administration of a single dose, with possible accumulation leading to abnormally high concentrations in the event of repeated administrations. For example, the elimination half-life of diazepam varies from 20 to 100 hours, and from 36 to 200 hours for its main active metabolite (desmethyldiazepam).

After metabolisation, benzodiazepines are mostly eliminated by the kidneys. Metabolisation and elimination speeds are highly variable across molecules, and, for a given molecule, across individuals. For prescription practice, it is usual to classify benzodiazepines into three categories regarding their elimination half-life: short, intermediate or long. The elimination half-life is a rough predictor of the duration of therapeutic effect. However, cut-offs vary according to sources; for example, the same molecule may be listed as “short” by one source and “intermediate” by another depending whether its active metabolites are considered or not.

2.1.3. Indications

The five main therapeutic indications of benzodiazepines result from their basic pharmacological properties:

- *Anxiolytic effect.* Benzodiazepines are indicated for the short-term management of acute and generalised anxiety disorders. According to international recommendations (*e.g.* those of the National Institute for Health and Care Excellence, NICE), treatment should not exceed 2-4 weeks, as antidepressants are indisputably a better option for long-term management of such disorders. Moreover, it has been shown that the efficacy of benzodiazepines decreases after 4 to 6 months,[73] being even not different from placebo in some studies. Molecules with an intermediate duration of effect are to be preferred in this indication. In any case, it is important to bear in mind that benzodiazepines do not treat the cause of anxiety and do not have antidepressant properties.

- *Sedative and hypnotic effect.* Benzodiazepines shorten the time needed to fall asleep, increase sleep time and reduce wakefulness. They should be used over a short period (2-4 weeks) *i.e.* to treat transient insomnia only. Longer treatments convey a risk of dependence. Moreover, benzodiazepines alter sleep cycles and worsen sleep quality by increasing the proportion of light sleep at the expense of deep sleep (slow wave sleep). Short-acting molecules are preferred when the problem is mainly time before falling asleep, while products with longer duration, *i.e.* intermediate, should be chosen in other cases.

- *Anticonvulsant and antiepileptic effect*. Owing to their potent inhibitory effect on the central nervous system, benzodiazepines are remarkably effective in preventing and treating epileptic seizures. Sadly, their use over a long period or as a chronic treatment of epilepsy is not feasible for at least two reasons: (i) the anticonvulsant effect decreases after a certain time, (ii) at the doses needed, adverse effects such as sedation, drowsiness make the treatment incompatible with daily life. *De facto*, their use is restricted to short-term prevention or treatment of conditions such as febrile seizures in children.

- *Muscle relaxing effect*. The strong muscle-relaxing properties of benzodiazepines can be useful in the treatment of muscle spasms. For this reason they have been used in some countries, such as France, in the management of acute lumbago. Their effectiveness was never clearly demonstrated and the poor benefit/risk ratio achieved makes their use in that indication obsolete.

– *Amnestic effect*. Acute administration, *e.g.* intravenous midazolam, of a sufficient dose of benzodiazepine induces a marked amnesia involving all the events and stimuli occurring during the period following administration. Independently of their muscle-relaxing effects, this property can be useful in surgery under local or regional anaesthesia.

There are many other indications of benzodiazepines, such as panic disorders (sublingual administration of short-acting molecules), management of alcohol dependency or of acute psychosis with hyper-excitability and aggressiveness. These will not be detailed here.

In brief, benzodiazepines are valuable tools for short-term management of various conditions in which they achieve rapidly a good level of efficacy with a relatively low toxicity in case of acute ingestion and poisoning. Most of their side effects ensue from unjustified chronic use.

2.1.4. Adverse effects

Sedation – sleepiness – fatigue

This effect, although useful in some therapeutic indications, is also the main concern and risk in others like management of anxiety. Indeed, benzodiazepines, at least over a given dose, induce irrepressible sleepiness and attention disorders which can be problematic in daily life, mainly when operating machines or vehicles.

Memory impairment

Even at doses commonly used to treat insomnia or anxiety, benzodiazepines can cause memory impairment. Acquisition of new information is impaired both by the deficit of concentration and attention induced by benzodiazepines and by their specific noxious effect on "episodic" memory (making subjects unable to remember recent events and their sequence in time). Other memory functions (*e.g.* remembering credit card and telephone numbers, words, and ancient memories) are not impaired.

Psychomotor adverse effects

Mainly if the dose used is too high and during the first days of treatment, benzodiazepines can impair perceptions and psychomotor coordination. For this reasons they increase the risk of falls and related fractures (hip, femoral neck), particularly in elderly persons. Several studies have concluded that the risk of fall-related injury was increased by about 40%,[74 75] which is a real concern when considering the absolute numbers. For example, in a country like France,

owing to exposure rate in persons over 65, an estimate as high as 10,000 fractures attributable each year to these treatments is not unlikely.[76]

Tolerance – Dependency – Withdrawal

- *Tolerance* to benzodiazepine effects can occur after some weeks of continuous use. In its typical form, the original dose becomes gradually less effective and would need to be increased to retrieve the magnitude of the original effect. Tolerance appears at different degrees and after different delays according to the type of molecule and indication.[77] For example, tolerance to the hypnotic effect seems to appear faster, *e.g.* after a few weeks, while tolerance to the anxiolytic effect seems much less rapid even if the efficacy of treatment after a few months is thought to be unproven.[73] Ashton noticed that long-term use could even exacerbate a pre-existing anxiety.[78] As mentioned before, tolerance to anticonvulsant effects makes benzodiazepine inappropriate for the long-term treatment of epilepsy. Tolerance does not seem to develop for effects on cognition and memory, with troubles often persisting after withdrawal; some long-term users may recover slowly but sometimes incompletely. Theoretically, because of tolerance, one would expect to observe a regular increase in the dose used in long-term treatments but several studies highlight that this is not the case.[79] [80]

- *Psychological and physical dependence* can appear after a few weeks or months of regular use, even at therapeutic doses. Difficulties in stopping the treatment are observed in most chronic users and are explained both by psychological dependence (psychological need to pursue the treatment) and by physical dependence mainly explained by withdrawal symptoms. These symptoms consist in an inversion of the pharmacological effects of benzodiazepines when the concentrations of the active molecule in target tissues fall under a given threshold. For this reason, brutal discontinuation of the treatment may induce severe generalised anxiety, insomnia, muscular spasms; headaches are frequent, confusion, hallucinations and coordination disorders can be observed. In the most severe cases, generalised seizures may occur. Withdrawal symptoms, which can be considered as a pharmacological effect, can be confounded with a rebound syndrome which is nothing more than the exacerbation of the disease treated after discontinuation of treatment. Differentiating between these two entities may be tricky. In general, dependence is more severe with short half-life molecules. Risk profiles for developing a dependence at therapeutic doses are provided in Table 4.

Table 4. Possible characteristics of subjects dependent on a therapeutic dose of benzodiazepines, Ashton Manual, 2002[81]

1. They have taken benzodiazepines in prescribed "therapeutic" (usually low) doses for months or years.
2. They have gradually come to "need" benzodiazepines to carry out normal, day-to-day activities.
3. They have continued to take benzodiazepines although the original indication for prescription has disappeared.
4. They have difficulty in stopping the drug, or reducing dosage, because of withdrawal symptoms.
5. If on short-acting benzodiazepines they develop anxiety symptoms between doses, or get cravings for the next dose.
6. They contact their doctor regularly to obtain repeat prescriptions.
7. They become anxious if the next prescription is not readily available; they may carry their tablets around with them and may take an extra dose before an anticipated stressful event or a night in a strange bed.
8. They may have increased the dosage since the original prescription.
9. They may have anxiety symptoms, panics, agoraphobia, insomnia, depression and increasing physical symptoms despite continuing to take benzodiazepines.

- *Withdrawal symptoms* can appear at the usual dose because of tolerance to the effects of the drug, mostly with short-acting ones or when stopping the drug abruptly or inadequately. In these conditions, a rebound of anxiety, insomnia and headaches are frequent, confusion and hallucinations can be observed, and more rarely vigilance trouble, lack of coordination and convulsion or coma in the most severe cases.

Paradoxical stimulant effects

A paradoxical stimulant effect can be observed, mainly in the two extremes of life and when high doses or intravenous injection are used. They consist in severe anxiety, irritability, aggressiveness, agitation, hallucinations, insomnia and nightmares and, even epileptic seizures.

Depression

Although frequently used with antidepressants in cases of associated anxiety or risk of suicide attempt, it is possible that benzodiazepines could cause or worsen depressive disorders. The mechanism of this unproven and debated effect remains unclear, although an interaction with neurotransmitters such as serotonin or norepinephrine could be plausible. Other hypotheses put forward the action of benzodiazepines on Brain-Derived Neurotrophic Factor (BDNF). In depressive patients without a specific treatment for depression, benzodiazepines could increase the risk of suicide attempt.

Abuse

Recreational use of benzodiazepines generally requires high doses associated with other substances. In the management of alcoholic withdrawal a severe dependence may appear when high doses of benzodiazepines are used over a long period, even when the treatment is

intermittent. In these cases, stopping the treatment is made complex by the risk of severe and serious reactions such as convulsions after withdrawal.[82]

2.2. Classification of benzodiazepines

Molecules are listed with their main indication and their dosage equivalences in Table 5.

Table 5. General characteristics of main benzodiazepines

	Market Aim	Half-life (hours)* [active metabolite]	Approximate equivalent oral dosage (mg)†
Benzodiazepines			
Alprazolam	anxiolytic	6-12	0.5
Bromazepam	anxiolytic	10-20	5-6
Chlordiazepoxide	anxiolytic	5-30 [36-200]	25
Clobazam	anxiolytic/anticonvulsant	12-60	20
Clonazepam	anxiolytic/anticonvulsant	18-50	0.5
Clorazepate	anxiolytic	[36-200]	15
Clotiazepam	anxiolytic	6-18	10-15
Diazepam	anxiolytic	20-100 [36-200]	10
Estazolam	hypnotic	10-24	1-2
Flunitrazepam	hypnotic	18-26 [36-200]	1
Flurazepam	hypnotic	[40-250]	15-30
Halazepam	anxiolytic	[30-100]	20
Ketazolam	anxiolytic	30-100 [36-200]	15-30
Ethyl loflazepate	anxiolytic	50-100	4
Loprazolam	hypnotic	6-12	1-2
Lorazepam	anxiolytic	10-20	1
Lormetazepam	hypnotic	10-12	1-2
Medazepam	anxiolytic	36-200	10
Midazolam	hypnotic	1-8	7.5
Nitrazepam	hypnotic	15-38	10
Nordazepam	anxiolytic	36-200	10
Oxazepam	anxiolytic	4-15	20
Prazepam	anxiolytic	[36-200]	10-20
Quazepam	hypnotic	25-100	20
Temazepam	hypnotic	8-22	20
Tetrazepam	muscle relaxant	3-26	100
Triazolam	hypnotic	2	0.5
***Non-benzodiazepines with similar* effects‡**			
Zaleplon	hypnotic	2	20
Zolpidem	hypnotic	2	20
Zopiclone	hypnotic	5-6	15
Eszopiclone	hypnotic	6	3

*Half-life: time taken for blood concentration to fall to half its peak value after a single dose. Half-life of active metabolite is shown in square brackets. This time may vary considerably between individuals.

†Approximate equivalent doses to 10 mg diazepam, proposed by Ashton.[81] These equivalents do not agree with those used by some authors. They are firmly based on clinical experience but may vary between individuals.

‡These drugs are chemically different from benzodiazepines but have the same effects on the body and act by the same mechanisms.

2.3. Data on usage in developed countries

2.3.1. Regulation

International guidelines recommend restricting the use of benzodiazepines to selected indications (*e.g.* severe and disabling or subjecting individuals to extreme distress) and short duration (no more than 12 weeks for anxiolytics and 4 weeks for hypnotics). That aims to minimize the risk of dependency and of withdrawal symptoms making discontinuation of treatment problematic.[82]

In the elderly, it is recommended to start with a dose that is half of what would be used in adults and to prefer molecules with a short, or if needed, intermediate elimination half-life in order to take into account age-related pharmacologic alterations (leading to an increased sensitivity to side effects).

2.3.2. Prevalence

We extracted various data from the literature about prevalence of use of benzodiazepines in the general population and in community dwelling elderly people. Comparisons across countries should be interpreted with prudence since many parameters can explain differences found:

- *Sample source.* Published data are extracted from various sources (general population, hospital records, cohorts, polls involving practitioners or pharmacists, sales statistics, etc.) and may not be comparable or not representative of the general population.
- *Period of data collection.* In a given country, prescription habits may be altered over time by the publication of recommendations, introduction or withdrawal of a new molecule or a new therapeutic class and many other events.
- *Duration of observation.* Some analyses rely on point prevalence, others on lifetime use or annual prevalence.
- *Types of molecules.* By definition, a drug utilisation study using data from a reimbursement database ignores molecules which are not reimbursed, as it is the case in Belgium and The Netherlands for a large proportion of benzodiazepines. Moreover, some studies do not consider similar products to benzodiazepines such as zolpidem, zopiclone.
- *Age distribution.* Ideally, to be valid, comparisons should be made on the basis of standardised samples.[83] Indeed, owing to the strong correlation between age and benzodiazepine use, differences across countries may simply be explained by a higher or lower proportion of elderly people in some countries.

2.3.2.1. Europe

France

A report published by the French Drug Agency (ANSM) in 2013 using reimbursement data for the whole population showed that about 14% of French inhabitants had used benzodiazepines at least once in 2012.[84] Prevalence was stable between 2007 and 2011 with a negligible decrease (1%) in 2011 and 2012 resulting from restrictions on the use of clonazepam. Among women aged 65 years and over, about one third had used at least one benzodiazepine for anxiety in 2012 and 18% had used one benzodiazepine indicated as hypnotic. In men, these frequencies were 16% and 11%, respectively. Mean durations of use were 4 months for anxiolytics (59% of treatments exceeded the recommended duration of 3 months) and 3.7 months for hypnotics (57% exceeded 3 months). While the doses of anxiolytics were slightly higher than recommended, the situation was clearly worse for hypnotics (35.6% of the prescriptions exceeded the recommended dose for adults and 33.2% in those aged 65 years and over).

A survey conducted between November 2007 and January 2008 among 350 French general practitioners concerning 2498 patients aged 65 years and older showed that the prevalence of benzodiazepine use was 32.1%.[85] The majority of patients had used benzodiazepines much longer than was recommended: 30.2% used them for 1 to 5 years and 38.2% for more than 5 years; only 15.1% were within the recommended duration, *i.e.* less than 3 months.

An earlier study conducted in a cohort of 2792 community-dwelling subjects 65 years and older living in the Gironde department, South-West France, found a prevalence of 31.9% for benzodiazepine use at inclusion in 1988-89.[86]

Spain

A study of the consumption of psychotropics in the Spanish population aged 65 years and over used data drawn from the 1993 and 2003 Spanish National Health Surveys, undertaken by the Ministry of Health and Consumer Affairs and covering 21,120 adults representative of the provinces and autonomous regions in 1993 and 2003.[87] The study included 3436 (non-institutionalised) individuals aged 65 years and older in 1993 and 6134 in 2003. Based on the results of this nationwide cross-sectional study, prevalence of anxiolytic or hypnotic use increased from 3.1% to 15.5% between 1993 and 2003.

This result was confirmed by the data derived from the European Study of Epidemiology of Mental Disorders (ESEMeD, 2000), a cross-sectional study of psychotropic drug use in Europe, showing that in a representative sample of 5473 non-institutionalised individuals aged over 18 years, randomly selected from the Spanish population, benzodiazepine one-year prevalence was 11.4%.[88]

Similarly, a Spanish Health Survey conducted in 2006[89] showed that 15.7% of subjects >15 years (n=24,660) and 24.1% of subjects ≥65 (n=6607) had used tranquilisers, muscle-relaxing or hypnotic drugs in the previous 15 days.

Italy

Data on use of psychotropics in Italy are scarce and ancient.

A study conducted between November 1992 and February 1993 by 62 general practitioners used a self-administered questionnaire on health status and drug use in a randomised sample of 3100 subjects 18 years and over. Prevalence of benzodiazepine use during the preceding week was 8.6% (11.8% for women and 5.0% for men). The prevalence was higher for the elderly aged 65 years and older (18.8%, 24.7% for women and 9.0% for men). 56% of benzodiazepine current users reported chronic use (daily, for more than 6 months). In the group of individuals 65 years and older, 70.1% of benzodiazepine users reported chronic consumption.[90]

Another study was conducted among 10,468 patients aged 65 to 84 years (women 59.2%) of 40 general practitioners living in North-Eastern Italy and selected on a voluntary basis.[91] Data about benzodiazepine use between 1st February and 31st July 2001 were extracted from a Health search database (including prescriptions) and a questionnaire administered by the general practitioner. Prevalence of use during the period was 21.5% (26.7% in women and 13.7% in men). 85.7% used only one benzodiazepine. The first prescriber was a general practitioner in 70% of cases, a hospital physician in 16.2% and a neurologist or psychiatrist in 9.7%. Prevalence of benzodiazepine use was associated with the presence of a chronic disease, such as stroke, coronary heart disease, cancer, the use of analgesics and antidepressants. Use was slightly higher in urban zones (23.5%) than suburbs or village areas (20.0%).

The Netherlands

In this country, measures to reduce over-prescription and chronic use of benzodiazepines were implemented in 2001. First, general practitioners were encouraged to limit the number of new prescriptions. Second, a computer programme was developed to assist pharmacists in identifying first time and repeated use and preventing chronic use. A study using a prescription database (*i.e.* Inter-Action Database, IADB) representative of prescribing practice, evaluated these measures and confirmed the expected gradual reduction of benzodiazepine use.[92] IADB includes information on pharmacy, prescriber or reimbursement status but not on over-the-counter drugs and in-hospital prescriptions. 382,000 individuals aged 20 to 84 years between 1998 and 2008 were included in the study. Average prevalence of benzodiazepine use per quarter year was 7.6% during the study period. Most of the users were women (68%). Prevalence decreased steadily over time (average prevalence of use per quarter year between

1998 and 2008 decreased from 5.4% to 4.5% in men and from 10.7% to 8.5% in women). The decrease was more marked after 2001 for both genders. Older age groups had higher prevalences of use, whatever the year or the gender considered. A decrease in benzodiazepine use was observed between 1998 and 2008 and was more marked in 2001 as was the case in the whole sample. Prevalence of use increased with age: 10.5% (65-69 years) and 16.0% (80-84 years) in 1998 *versus* 7.5% to 14.0% in 2008. For women, prevalences were 22% (60-64 year age group) and 32.0% (80-84 year age group) in 1998 *versus* 15.0% and 25.0% in 2008 for the whole 60-84 year group.

Sweden

A study was conducted using the Swedish Prescribed Drug Register containing individual data for all prescriptions dispensed to the whole population of Sweden (about 9 million inhabitants). Elderly individuals aged 75 years and older registered in the SPDR from October to December 2005 were included (n=731,105 corresponding to 91% of the concerned population). The mean age was 82 years, 62% of the sample were women. During the observed period 25% of individuals had used one or more benzodiazepine or related drugs, with 19% using an association of two or more molecules. Short-acting molecules (*i.e.* zopiclone, zolpidem, zaleplon) were the most prescribed (65.5% of benzodiazepine prescription). Among benzodiazepine users 22% had received a prescription for long-acting molecules (*i.e.* clonazepam, diazepam, flunitrazepam, nitrazepam) and 26.6% for medium-acting ones (alprazolam, lorazepam, oxazepam).[93]

United Kingdom

A study used the 1946 British birth cohort database, which followed 3299 individuals for 22 years (1977 to 1999, age of participants increasing from 31 to 53), to describe the consumption of psychotropics (antidepressants, anxiolytics, hypnotics) and their association with common mental disorders. Benzodiazepine annual exposure was measured four times during the follow-up and increased from 3.1% to 5.9% as the participants aged.[94]

A phone survey was conducted in June-October 1994, among 4972 non-institutionalised individuals aged 15 years and over. Only 0.8% of the total sample (1.9% for 65 years and older) declared current use of anxiolytics (more than 90% being benzodiazepines) and 1.5% (5.2% for 65 years and older) declared current use of hypnotics. Chronic use (more than one year) was reported by 47.4% of anxiolytic users and by 61.3% of hypnotic users. Prescriptions were generally made by general practitioners. Interestingly, antidepressants were often prescribed for sleep and anxiety disorders.[95]

Germany

As in the UK, the use of psychotropic drugs appeared to be lower in Germany compared to other European countries and does not seem to represent a major concern in this country. This could explain why data about benzodiazepine use are scarce and relatively ancient.

A first study used the data of the National Health Interview and Examination Survey of non-institutionalised adults, collected between October 1997 and March 1999.[96] Among the randomly sampled participants (n=1605), aged 60 years and older (54.8% being women), the prevalence of benzodiazepine use was 3.7% (2.3% as anxiolytics and 1.4% as hypnotics). 61.6% of anxiolytic users and 54.8% of hypnotic and sedative users declared a long-term consumption (>3 years).

One other study used a random sample of individuals aged 20 to 79 years living in a rural and urban area of North Eastern Germany (Study of Health In Pomerania) between 1997 and 2001.[97] The study initially aimed to assess the relation between sedative, anxiolytics, hypnotics, opioid medication and tobacco and alcohol consumptions. Drug intake in the 7 days before the interview, conducted in a health examination centre, was assessed by inspecting drug packages if feasible or according to information about drug names provided by the patient. Among men, the one-week prevalence of sedative, anxiolytic or hypnotic use was 2.1% (3.8% in the 60-79 year group). For women, the prevalence was 3.5% (6.8% in the 60-79 year group). Prevalence for overall benzodiazepine use was not given. The definition included benzodiazepines and related drugs but also other hypnotics and sedatives (*e.g.* barbiturates, carbamates). The results were roughly similar to those of the previous study suggesting that prevalence of use was not markedly modified by age.

The remarkably low prevalence of benzodiazepine use in Germany may have several explanations:

- Specificities in regulatory and administrative procedures controlling psychotropic use, which are stricter than in other European countries.[96]
- In general, German people tend to have a negative feeling towards psychopharmacotherapy,[98 99] beyond the limited use of psychotropic drugs that may also play on the probability of diagnosing a mental illness. In any case, the prevalence of mental disorders reported in Germany appears lower than in other European countries.[100]
- A reverse association between psychotropic drug use and alcohol consumption is classically admitted and Germany is one of the countries with the highest levels of alcohol consumption in the world.[96 101 102]

2.3.2.2. North America

USA

A study conducted in the US in 2008 and using prescription data from a database including around 60% of all retail pharmacies in the USA (IMS Health Inc.)[103] concluded that 5.2% of adults from 18 to 80 years had filled one or more benzodiazepine prescriptions in the year, the prevalence increasing with age (2.6% in the group aged 18-35 years to 8.7% in the group aged 65-80 years). Benzodiazepine use was nearly twice as prevalent in women as men. Prevalence of long-term use (≥120 days) increased with age: 14.7% (18-35 years) *versus* 31.4% (65-80 years). Conversely, the proportion of prescriptions issued by psychiatrists decreased with age (15% in the 18-35 group *versus* 5.7% in the 65-80 group). In all age groups, about one quarter of users had received long-acting benzodiazepines.

Canada

A study conducted using the drug product information network database in the state of Manitoba concluded that the prevalence of benzodiazepine use in the general population (6.1%) remained stable between 1996-97 and 2011-12 but increased for Z drugs (1.1% to 3.7%). In the group 65 years and older, the prevalence of use decreased for benzodiazepines (17.5% to 12.6%) and increased in a higher proportion for Z drugs (2.5% to 9.4%). In the overall sample, 80% of the prescriptions issued from general practice. This information was not available for the elderly.[104]

A study was conducted among British Colombia residents registered in the provincial health insurance plan in 1996 and 2006 (covering 88% of the population in 1996 and 92% in 2006) to examine changes in patterns of benzodiazepine use over this period during which evidence of harm associated with long-term use became more publicised.[105] About 4 million individuals participated in the 2006 evaluation. 8.4% used benzodiazepines and related drugs (4.9% for less than 100 cumulative days within a year and 3.5% for more than 100). Among 65 years and older, about 23.1% had used benzodiazepines at least once in 2006 (9.8% in the short-term and 13.3% in the long-term). Use and long-term use increased from 1996 (7.8% and 3.1%, respectively). The same trend was observed in the elderly.

More ancient data from Hogan *et al.*[106] showed a prevalence of 25.2% to 26.4% for the 1990-1996 period. Subjects with a diagnosis of depression were more often treated with benzodiazepines (37%) than with antidepressants (26.9%).

Similar figures were found in Ontario (over 1 million residents over 65) where prevalences decreased slightly between 1993 (25.1%) and 1998 (22.5%). There was a trend for switching more frequently towards antidepressants (8.5% in 1993 and 10.2% 1998) and for preferring

short-acting (<24 hours) molecules, the short-acting/long-acting ratio increasing from 3.6 to 5.8 between the two dates.[107]

2.3.2.3. Asia-Oceania

Australia

The National survey of Mental Health and Wellbeing, a nationwide representative sample conducted in 2007 among 8841 community Australians aged 16 to 85 years, showed that the prevalence of anxiolytic, hypnotic or sedative drugs used in the 2 weeks preceding the interview was 4.7%.[108]

An Australian study[109] was conducted among 3970 individuals aged 65 years and more registered in a general practice database (*i.e.* Medical Enquiry Drug information Center-General practice, MEDIC-GP database) in 2002. One-year prevalence of benzodiazepine and related drug use was 15.7%.

Taiwan

In a dynamic sample of one million individuals randomly selected from the National Health Insurance of Taiwan, annual prevalence of anxiolytic-hypnotic use in Taiwan was estimated to be over 20% between 2002 and 2009.[110] In 2002, a study included 4,267 individuals aged 65 years and older registered in the sampling database from the Bureau of National Health Insurance (BNHI) (approximately 50,000 individuals randomly selected from the eligibility files of the National Health Insurance programme in Taiwan). One-year prevalence of benzodiazepine use was 43%.[111] In the year studied, 35.3% of users had received benzodiazepine for more than 4 months and 21.7% for more than 7 months.

2.3.3. Patterns and characteristics associated with benzodiazepine use in the elderly

2.3.3.1. Characteristics associated with ever use

Characteristics associated with benzodiazepine use in an elderly population have been largely documented. Among others, they consist of:

- *Socio-economic factors:* female gender[112 113] and older age[113 114] are unanimously reported in literature; lower educational level[32 33] or income[113] are also often found associated.

- *Lifestyle factors:* low-skilled occupations or sedentary living,[115] loneliness,[116] urban living,[93] smoking,[116] low[116] or high[117] consumption of alcohol, lower consumption of wine.[93 118]
- *Health conditions:* chronic diseases[86 119] such as cardiovascular disease, cancer, chronic pulmonary disease or arthritis,[120] polypharmacy,[116 121] and, obviously, conditions that are indications for prescribing benzodiazepines: insomnia,[122] depression,[112] and anxiety.[123]
- *Negative subjective perception of health.*[122 124]
- *Use of other psychotropic drugs.*[93 117]
- *Interaction with medical practitioners:* higher numbers of doctor's visits,[119] proximity to doctor's practice.[122]
- *Higher level of dependency*.[113]
- *Cognitive decline*, at least for psychotropics in general.[122]

2.3.3.2. Characteristics associated with chronic use

Chronic use, often quite prolonged, is frequent for benzodiazepines, particularly among women[116 125] and the elderly.[123] Other factors include: smoking,[116 123] polymedication,[116] depressive symptoms,[126] use of antidepressants, sleep disorders,[123] systemic hypertension,[126] painful arthrosis,[126] poor physical health perception,[126 125] alcohol consumption,[123] severe anxiety,[127] previous use of benzodiazepines indicated as hypnotic,[126] prescription initiated in hospital.[128 129] Living alone[126] and physical activities[123] were negatively correlated with chronic use. A drug dependence profile could also play a role in long-term use.[125]

3. Potential relationship between benzodiazepine use and dementia

3.1. Reasons for interest

Benzodiazepines are widely used to treat anxiety and sleep disorders; they are frequently coprescribed with antidepressants. Prevalence of use is consequently high in most developed countries, particularly in women and the elderly.[117 130 131] Moreover, despite international guidelines recommending short duration uses to minimise the risk of dependency and withdrawal symptoms,[82] usage is more often chronic, particularly in elderly persons.[131-133] Apart

from other risks such as falls and fractures,[76] the putative deleterious effects of chronic consumption of these drugs on cognitive functions have been advanced, particularly in the elderly owing to their high neurocognitive vulnerability.[134] There are several arguments for researching a potential relationship between benzodiazepine use and risk of dementia:

- First, there is a certain biological plausibility: benzodiazepines are known to induce central nervous inhibitory effects and can induce short-term amnesia or confusion;[135 136] they have also been suspected of increasing the risk of cognitive decline.[137 138]

- Second, if benzodiazepine use actually increased the risk of dementia, the resulting public health impact would be major: (i) dementia is currently one of the main causes of invalidity in old age, its societal burden will become even greater in the coming decades with the ageing of the population,[3 4] (ii) considering the high prevalence of both benzodiazepine use and dementia, a causal association, even in a multifactorial pathway, would result in a significant proportion of cases in excess with tremendous consequences, owing to the seriousness and societal cost of the disease.

- Finally, since therapeutic options remain rather limited, identifying potentially alterable risk factors is crucial.

3.2. Possible sources of information for researching a putative association

3.2.1. Pharmacovigilance databases

Pharmacovigilance systems focus on the post-marketing surveillance of risks associated with drugs. As, clinical trials conducted before approval only include limited samples of patients (generally under 3000), it is consequently not possible to detect unusual side effects. In addition, patients included are strictly selected according to several criteria and for that reason do not reflect the whole range of situations encountered in real life.

Obvious limitations of pharmacovigilance databases for obtaining valuable information about a potential relationship between benzodiazepines and dementia are mainly due to the probably huge under-reporting of an association such as dementia which may occur several years after initiation of a treatment. Indeed, (i) cognitive disorders are likely to be largely under-diagnosed and are known to be particularly under-reported, (ii) use of benzodiazepines is almost considered as “normal”, particularly in the elderly, and because of this their adverse effects are often ignored, (iii) owing to the long delay between starting the treatment and the suspected risk, it is quite unlikely that a case-by-case analysis can identify an association, if any exists.

3.2.2. Experimental studies

In experimental studies the investigator assigns and controls exposure by means of randomisation. Subjective biases are neutralised by making patients and investigators blind to the exposure status. If properly designed and conducted, these studies can achieve the highest level of proof in assessing a causal association. Indeed, all putative confounders (*a priori* known or unknown) are neutralised by the randomisation of exposure across the groups compared. For this reason, this design remains the gold standard for testing efficacy (and safety) of new drugs or new therapeutic procedures. Sadly, using such an approach in the context of benzodiazepines and dementia would be ethically unacceptable. In short, it would mean deliberately exposing and not exposing for at least 10 years and without considering therapeutic justifications, two large samples of subjects with the aim of comparing them with regards to a risk possibly caused by exposure.

3.2.3. Observational studies

Unlike experimental studies, in non-experimental studies the investigator does not control for the reasons and circumstances of exposure. Consequently, the absence of random assignment of exposure conveys the risk of several biases, mainly confounding bias, even if this bias can be in part neutralised by several statistical procedures (matching, adjustment, etc.). There are two main types of non-experimental design: cross-sectional and longitudinal studies, which are themselves split into prospective studies (*e.g.* cohort studies, comparative or not) and retrospective studies (comparative or not, the first being called case-control studies). Cross-sectional studies in their classical form are purely descriptive and only provide the point-prevalence of a given characteristic (disease, opinion, drug use, etc.). Longitudinal studies (*i.e.* cohort or case-control studies) seem to be the only promising approach to use for the present purpose. Cohort and case-control studies are compared regarding methodological and feasibility considerations in Table 6.

Table 6. Conditions influencing the choice of the design in observational studies

	Cohort studies	Case-control studies
Comparison groups	According to the exposure status (exposed or not)	According to the diseased and non-diseased status. Feasibility depends upon the expected incidence of the disease during the study period (cases) and the possibility of finding adequate disease-free controls
Observation	Prospective (from exposure to event) during a certain period time or till onset of the event studied	Retrospective (backward, from event to previous exposure researched in a defined time-window)
Measurement	- Incidence of the event in each comparison group - Incidence ratio between comparison groups (*e.g.* relative risk, RR) - Risk according to different levels of exposure	- Prevalence of the suspected risk factor in the pre-defined time-window compared across diseased and non- diseased groups - Odds ratio (ratio of exposure odds in diseased and non-diseased groups) being a satisfactory approximation of RR when the disease studied is rare
Benefits	- *A priori* adapted to rare exposures - Possibility of studying the time-course between exposure start and outcome - Possibility of studying several outcomes - Best conditions for RR computation	- Adapted to rare outcomes - Adapted to outcomes with a long latency period - Sample size required are often limited - Possibility of studying several risk factors
Drawbacks	- Loss to follow-up - Large sample sizes generally needed - Long follow-up often needed - Generally expensive (except for historical cohort studies) - Studying several risk factors or different types of exposure is often complex, if not impossible - Difficult to use, if not impossible, for outcomes with a low incidence	- Missing values concerning the exposure status - Exposure ascertainment possibility affected by numerous biases (*e.g.* recall bias) - Selection of adequate controls is complex (representativeness, selection bias) - Does not allow direct computation of RR - Not adapted to low levels of exposure
Indications	**- Frequent events** **- Rare exposures** **- One exposure, several outcomes** **- Higher level of proof (possible to study the temporal relationship between exposure and outcome in good conditions)**	**- Rare events** **- Frequent exposures** **- Several exposures, one outcome**

RR=Relative Risk.

4. General methodological considerations for evaluating the relation between benzodiazepines and dementia

Studying the relation between benzodiazepines and dementia is a real methodological challenge:

- First, since a randomised controlled trial is not ethically acceptable, causality can only be inferred from observational designs which are always questionable for this purpose.

- Second, since the strength of the association is expected to be in the order of 2 or lower, reaching statistical significance, particularly when intending to control for several potential confounders, may be problematic.

- Third, dementia has a long latency period (not precisely known but assumed to be at least 10 years). Therefore, a study aiming to evaluate the plausibility of a causal link should consider variables like drug treatments or other risk factors to be researched over a decade or more before the diagnosis of the disease, which requires an unusually long follow-up.

- Fourth, despite being somewhat contradictory, the literature data show that a higher prevalence of anxiety, insomnia or depression may be observed in the years preceding the diagnosis of Mild Cognitive Impairment (MCI) or dementia.[29 139 140] Unfortunately, no precise chronology can be used to establish when the onset of such a symptom is too early to be a prodrome. This issue is crucial since these symptoms correspond to the main reasons for prescribing benzodiazepines, which fuels the possibility of a prothopathic bias, or reverse causation, *i.e.* benzodiazepines not being the cause of the disease but being prescribed because of its first signs.

- Finally, as the strength of the association between benzodiazepine use and dementia is expected to be low, controlling for potential confounders is crucial and requires precise and reliable information on numerous variables.

5. Summary

- Dementia is a major Public Health concern as it accounts for a major burden worldwide which will become even greater in the coming decades with population ageing.

- Since there is currently no treatment for dementia, the identification of putative modifiable risk factors seems crucial.

- The question of a potential causal link between benzodiazepines and dementia is a key question linked with its plausibility and with its potential high impact.

- Studying the link between benzodiazepines and dementia raised challenging methodological considerations.

- Research into this putative link should be focused on the data coming from longitudinal observational studies.

- The questions are: (i) Are there observational studies already developed on the topics? (ii) What kind of information can they provide? (iii) Is this information useful in elucidating the question about the link between benzodiazepines and dementia risk?

PART II - Review of studies looking for a link between benzodiazepine use and dementia

1. Context and objective

1.1. The context in a few questions

WHAT DO WE KNOW?

In most countries, benzodiazepine consumption is high and often chronic, particularly in elderly populations, regardless of good practice guidelines (cf. Part I).

Their short-term deleterious effects on cognition and memory are well established. Worryingly, several studies have concluded that there is an increased risk of cognitive decline, at least in chronic users (cf. Part I).

Considering the high prevalence of both benzodiazepine use and dementia, a causal relationship between these two events would have a dramatic impact in terms of number of cases in excess and tremendous consequences with regards to the seriousness and cost of the disease (cf. Part I).

WHAT DO WE NOT KNOW?

If this association was proven, benzodiazepine use would typically be an alterable risk factor of dementia. As treatment options remain limited, identifying alterable factors contributing to dementia is crucial. The pending issue remains the nature, causal or not, of the association, if any, observed between benzodiazepine use and dementia. To progress further, we performed a review of all the pharmacoepidemiological studies that have assessed this association. To our best knowledge, no such a review was currently available.

1.2. Objective

We aimed to identify, assess and compare relevant works published to date that have studied the relation between benzodiazepine exposure and the subsequent risk of dementia and to discuss the validity of their conclusions after having weighted and ranked their intrinsic quality by means of an operational scale. Here we present the methodology used to identify previous observational studies on the topic, summarise each of them, and evaluate their quality. The main results will be provided and several points will be discussed:

(i) Do the results of the studies reviewed converge towards a global judgment about the link between benzodiazepine use and dementia (*i.e.* were the results congruent)?

(ii) Does this global judgment, if any, seem to be valid and robust or possibly jeopardized by methodological flaws or an insufficient level of knowledge?

(iii) Is there a need and are there opportunities for conducting new studies? For example, are there unsolved questions, limitations identified in the studies that could lead to the development of new approaches in order to improve our knowledge about the nature of the relationship between benzodiazepines and dementia?

2. Methodology

2.1. Search strategy

A search in the Medline database was performed to identify all original pharmacoepidemiological studies (cohort or case-control) published in English between January 1st 1992 and January 1st 2012 which explored the relationship between benzodiazepine use and dementia in the general population (middle-aged or elderly individuals). A list of *Medical Subject Heading* (*MeSH terms*) and a complementary list of key words were used to identify these studies (Table 7). References cited in the selected papers were also systematically reviewed to ensure that no relevant study on this topic could have been ignored.

Table 7. Research terms used to identify studies on the relationship between benzodiazepine use and dementia risk

((dementia[MeSH Terms] OR alzheimer disease[MeSH Terms] OR dementia[Title/abstract] OR alzheimer[Title/abstract]) AND (benzodiazepines[MeSH Terms] OR anti-anxiety agents[MeSH Terms] OR (hypnotics and sedatives[MeSH Terms]) OR benzodiazepine*[Title/abstract] OR tranquilizing agents[MeSH Terms]) AND (prospective studies[MeSH Terms] OR cohort studies[MeSH Terms] OR case-control studies[MeSH Terms] OR longitudinal studies[MeSH Terms] OR cohort stud*[Title/abstract] OR case-control stud*[Title/Abstract] OR longitudinal stud*[Title/Abstract]))

Characteristics of the studies eligible for the review are summarised in Table 8.

Table 8. Inclusion criteria of studies on the link between benzodiazepine use and dementia

Characteristics	Inclusion criteria
Design	Observational, longitudinal studies (cohort or case-control)
Study population (main characteristics)	Human beings General population Age, sex, racial or ethnic group unspecified. No diagnosis of dementia during observation period for exposure
Study Population (geography)	Developed countries: North America, West Europe, Australia, New Zealand, South Korea, Israel, Japan, Singapore, Taiwan
Exposure	Benzodiazepine exposure measured before the diagnosis of dementia
Event	Dementia
Language	Studies published in English
Period	1st January 1992 to 1st January 2012

2.2. Summarising the studies

The following information was extracted: study design, sampling method, follow-up, definition and assessment of exposure, definition and assessment of dementia, confounding factors, main results.

2.3. Quality assessment of the studies

We used the Newcastle-Ottawa scale, specifically developed for non-randomised studies and considered as one of the two most useful tools for systematic reviews and meta-analysis.[141] Each study is judged according to three broad perspectives: (i) selection of the study groups, (ii) comparability of groups, and (iii) ascertainment of either the exposure (case-controls) or the outcome of interest (cohorts). A maximum of 9 stars is allocated to the highest quality studies.[142]

3. Results

3.1. Description of the studies identified

Out of the 350 references retrieved through the literature search, 6 fulfilled our criteria (Table 9).

Table 9. Result of literature search about "benzodiazepine use and dementia"

Author	Date	Journal	Study design
Fastbom *et al.*[10]	1998	*Alzheimer Disease and Associated Disorders*	Cohort
Lagnaoui *et al.*[7]	2002	*Journal of Clinical Epidemiology*	Case-control
Lagnaoui *et al.*[6]	2009	*Age and Ageing*	Case-control
Wu *et al.*[5]	2009	*American Journal of Geriatric Psychiatry*	Case-control
Wu *et al.*[8]	2011	*American Journal of Geriatric Psychiatry*	Case-control
Gallacher *et al*.[9]	2011	*Journal of Epidemiology and Community Health*	Case-control

These studies are summarised in Table 10 and are briefly discussed below in chronological order of publication.

3.1.1. Study by Fastbom et al., 1998

The first work on the putative effect of benzodiazepines on the risk of dementia was published by Fastbom *et al*.[10] in 1998. Rather than looking at a deleterious role, these authors were interested in the role of GABA receptors in the neuroprotection process and therefore in the putative beneficial effect of benzodiazepines on the risk of dementia. Their study was conducted on the Kungsholmen cohort which, since 1987, had included a random sample of individuals aged 75 years and older, institutionalised or not and registered in a parish of Stockholm (Sweden). At the end of a 3-year follow-up, 75 chronic users of benzodiazepines were compared to 167 non-users regarding the risk of dementia (all types according to the DSM-III-R criteria[143]). Secondarily, the risk was assessed separately for the Alzheimer type. The authors concluded that benzodiazepines had a significant protective effect on the risk of dementia (all types) and Alzheimer's disease. This effect, which would appear today as paradoxical, could be partly explained by the inclusion of past-users of benzodiazepines in the reference group. Indeed, discontinuation may have been justified by incipient dementia. Interestingly, according to several studies reviewed below, an association with an excess risk of dementia was found for patterns of exposure corresponding to the past-user group as defined in this study.

3.1.2. Study by Lagnaoui et al., 2002

The first study focusing on the putative deleterious effect of benzodiazepines on the risk of dementia was published in 2002 by Lagnaoui *et al.*[7] These authors conducted a nested case-control study on the PAQUID cohort of 3777 individuals aged 65 years and older who were not institutionalized and were randomly selected from the general population registered in the electoral lists of Gironde and Dordogne, two administrative areas in South-West France,

between 1987 and 1989. During the 8-year follow-up, 150 cases of dementia (all types) were diagnosed and compared to 3519 matched dementia-free controls with regard to previous exposure to benzodiazepines and related drugs. Drug exposure and cognitive functions (including dementia diagnosis) were evaluated at inclusion and then cross-sectionally every 2-3 years. The diagnosis of dementia was particularly robust and confirmed by a senior neuro-geriatrician. During the whole follow-up, dementia risk was found increased in former users of benzodiazepines (defined by exposure ended at least 2-3 years before the dementia diagnosis) compared to non-users (no use before the date of diagnosis of dementia of the matched case). Adjusted Odds Ratio (OR) was 2.3 (95%CI 1.2 to 4.5). The authors found no excess risk in current users (defined by the use of benzodiazepines at the date of dementia diagnosis and/or during the 2-3 preceding years). One cannot exclude that the association found in the former users group could be in part explained by the discontinuation of the treatment motivated by the onset of a cognitive decline or other symptoms possibly linked to a dementia not diagnosed at this date. The current users group combined several patterns of use with putative differences regarding their risk of dementia: (i) benzodiazepines recently prescribed to treat early signs of dementia (*i.e.* anxiety, depression or insomnia), this pattern corresponding to a protopathic bias; (ii) recent use not related to the symptoms of dementia; (iii) treatments started long before and conveying a risk of a depletion of susceptible bias. The PAQUID programme did not provide precise information about doses or durations of exposure, two important parameters for identifying potential at risk uses (*i.e.* chronic use, episodic) or a dose-effect relationship.

3.1.3. Study by Lagnaoui et al., 2009

Seven years later (2009), Lagnaoui *et al.*[6] published another case-control study nested in a representative sample of 3903 women aged 65 years or more living in a community or institution in the Canadian province of Quebec and participating in the Canadian Study of Health and Ageing (CSHA) in 1991-1992. The objective was to evaluate the relation between benzodiazepines or related drug use and the subsequent risk of both dementia of all types and Cognitive Impairment No Dementia (CIND) measured five years after inclusion. Out of the 510 women included in the study, 73 (14.3%) cases (combining 14 dementia of all types and 59 CIND) were compared to 437 controls regarding previous exposure to benzodiazepines or related drugs registered in the reimbursement list of the Health Insurance Scheme in Québec (Régie de l'Assurance Maladie du Québec, RAMQ). As in their previous study,[7] the authors found an increased risk of dementia or CIND in former users (defined by a drug dispensation found on at least one date before diagnosis but not in the year preceding this date) compared to non-users. Owing to the limited number of cases, this excess risk was not statistically significant

(OR 1.5, 95%CI 0.6 to 3.4). No increase in risk was found for current use (defined as at least one dispensation during the year preceding the index date). The same remarks can be made as above regarding the definition of exposure patterns. However, this study suffered from three other limitations: (i) the case definition combined two entities (dementia and CIND) which possibly have different pathophysiological mechanisms, (ii) putative prodromes of dementia, such as depression, were apparently not considered in the adjustment model, and (iii) the follow-up (ranging from 2 to 5 years) remained short regarding the latency period of the disease, which is thought to be long.

3.1.4. Study by Wu et al., 2009

The same year, Wu *et al.*[5] published the results of a case-control study conducted on a 1% random sample of the National Health Insurance Research Database (NHIRD) encompassing about 97% (22 millions individuals) of the Taiwanese population. The study included 779 subjects diagnosed with dementia (all types) between 2000 and 2004, aged 45 years and older (mean age: 76 years), and followed-up for 4 to 8 years. These cases were age and sex matched with 4626 subjects without dementia. The authors concluded that there was an increased risk of dementia in benzodiazepine users. Compared to cumulative uses of less than 90 days or cumulative dosage of less than 90 Defined Daily Doses (DDDs), long durations of exposure and high cumulative dosages were associated with a higher risk of dementia (OR 1.38, 95%CI 1.03 to 1.83 for a cumulative exposure of 90 to 179 days, 1.45 (1.18 to 1.79) for 180 days and over, 1.28 (0.97 to 1.68) for cumulative dosage of 90 to 179 DDDs and 1.39 (1.12 to 1.73) for cumulative dosage of 180 DDDs and over). The possibility of a protopathic bias cannot be ruled out since past and recent initiations of benzodiazepines were not analysed separately. The authors tested the plausibility of this bias by a sensitivity analysis consisting of excluding zopiclone and zolpidem (often prescribed in insomnia) from the exposed group, but this did not alter the results. This strategy suffers from some obvious limitations and did not consider other reasons for prescribing benzodiazepines possibly related to early signs of dementia, such as anxiety or depression and even insomnia treated with benzodiazepines.

3.1.5. Study by Wu et al., 2011

In 2011 Wu *et al.*[8] published a second case-control study conducted with the data from the Longitudinal Health Insurance Database (LHID), a representative sample of 1 million individuals randomly extracted from the previously mentioned NHIRD. Subjects were aged 45 years or more and the maximum follow-up was 11 years (1997-2007; mean 9.1 years). A large number

(8434) of cases (dementia of all types) were identified and matched on age, gender and duration of follow-up with 16,706 controls. Cases and controls were compared regarding current use (defined as a reimbursement in the 15 days preceding the diagnosis of dementia) and former uses (treatment discontinued for 16 days to 1 year, 1 to 2 years, 2 to 3 years, and more than 3 years) *versus* no use during the follow-up. They also considered the cumulative dose used during this follow-up (1-89 DDDs, 90-359 DDDs, ≥360 DDDs). After taking into account several risk factors for both benzodiazepine use and dementia (including potential prodromes such as anxiety, depression and sleep disorders), the authors concluded that current use of benzodiazepines (whatever the cumulative dose) was associated with a higher risk of dementia (OR 2.71, 95%CI 2.46 to 2.99) than non-use (reference) and former use. For the latter group, the magnitude of the odds ratio decreased (significant correlation) with the lapse of time since discontinuation: 1.68 for less than 1 year; 1.23 for 1-2 years; 1.22 for 2-3 years, and 1.08 for >3 years. From these figures, they suggested that the association between benzodiazepine exposure and an increased risk of dementia could be reversible in short-term users (after 1-2 years for an exposure of 1-89 DDDs) and in medium-term users (after 2 to 3 years for an exposure of 90-359 DDDs) but not in heavy users (≥360 DDDs). For heavy users, the risk continued to be significantly increased by 65% more than 3 years after discontinuation. Despite the long follow-up available, the possibility of reverse causation (protopathic bias) remains as the method used did not exclude subjects in whom benzodiazepines had a good chance of having been prescribed because of the prodromes of a dementia, as suggested by the higher value of the odds ratio found in current users, including recent initiators. Protopathic bias seems less likely and the results appear more convincing for former users who have stopped their treatment for 3 years or more, especially those with a cumulative exposure of 360 DDDs and more. This large study was the first to look for a dose-effect relationship and to compare the effect of discontinuation on the ability to recover cognitive abilities.

3.1.6. Study by Gallacher et al., 2011

The same year, Gallacher *et al.*[9] published a case-control study using data from the Caerphilly Prospective Study. Between 1979 and 1983, about 3000 men born between 1920 and 1939 in Caerphilly, a small town in South Wales (UK), and roughly representative of the aged population of this area, were included and medically examined at intervals of 5-6 years. At the most recent date available, 1134 men (69.4% of the survivors) with durations of follow-up from 19 to 24 years (average: 22 years) were eligible for the study. As the medical follow-up included an extensive screening of both cognitive impairment and dementia, 93 men presenting with dementia (all types, 44 vascular and 49 non-vascular) were compared with 866 men without

dementia with regard to benzodiazepine use. The authors concluded that there was an increased risk of dementia in *ever users* (OR for all types of dementia 3.10, 95%CI 1.33 to 7.23 / OR for vascular dementia 3.24 (0.98 to 10.72) / OR for non-vascular dementia 3.34 (1.10 to 10.18)). Adjustment for anxiety and sleepiness did not markedly alter the results. No dose-response effect was apparent. The association was strongest for men treated for an estimated cumulative duration of 4 years or less (OR for all types of dementia 4.38 (1.15 to 16.75)) but remained noticeable, although not statistically significant, in those having a cumulative use of more than 4 years (OR for all types of dementia 2.31 (0.74-7.20)). Interestingly, the odds ratio was 4.19 (not significant: 95%CI 0.90 to 19.49) for the small group of men who had started the treatment 13 to 22 years before the onset of a dementia of the non-vascular type but the odds ratio was smaller for more recent initiation (OR 2.03 (0.38-10.75)). The contrary was observed for vascular dementia: odds ratios, which were not significant, were smaller for earlier use than for recent use: 1.45 (0.13 to 16.27) and 4.25 (0.94 to 19.17), respectively. The undisputable added value of Gallacher's study was its access to a very long follow-up, allowing the effect of treatments initiated long before the onset of dementia to be explored, which is a sensible way to minimise the plausibility of a reverse causality. Unfortunately, its limited sample size and the rather low benzodiazepine consumption in this UK male population precluded any statistical significance for several of the most relevant sub-analyses conducted to assess the plausibility of protopathic bias.

3.1.7. Summary of the studies (Table)

The main characteristics of these studies are summarised in Table 10.

Table 10. Studies having assessed the relationship between benzodiazepine use and dementia

Study	Number of participants (age)	Study duration	Dementia definition and (measurement)	Confounders	Association between benzodiazepines and dementia (Odds Ratios, OR)
Kungshomen study, Sweden (Fastbom *et al.*1998[10]) *Cohort study or case-control study?*	242 (≥75 years)	3 years	Dementia all types, Alzheimer's disease (DSM-III-R criteria)	Age, gender, educational level, exposure to non-steroidal anti-inflammatory drugs, exposure to oestrogens	*Chronic use:* . 3 years use *versus* < 3 year use: estimated non adjusted OR=0.40
PAQUID study, France (Lagnaoui *et al.* 2002[7]) *Case-control study*	3300 (≥65 years)	8 years	Dementia all types (DSM-III-R criteria)	Age, gender, educational level, living alone, depressive symptoms, history of psychiatric diseases, wine consumption	*History of use:* . ever use *versus* never use: OR=1.7 (1.2-2.4) . current use *versus* never use: OR=1.0 (0.6-1.6) . former use *versus* non-users: OR=2.3 (1.2-4.5)
Canadian study of Health and Aging, Quebec (Lagnaoui *et al.* 2009[6]) *Case-control study*	510 women (≥65 years)	5 years	Dementia all types (ICD-9 code)	Age, educational level, activities of daily living scale, institutionalisation, number of drugs used, exposure to non-steroidal anti-inflammatory drugs, exposure to oestrogens	*History of use:* . current use *versus* non-use: OR=1.0 (0.5-2.0) . former use *versus* non-use: OR=1.5 (0.6-3.4)
National Health Insurance Research database study, Taiwan (Wu et *al.* 2009[5]) *Case-control study*	5400 (≥45 years)	8 years	Dementia all types (ICD-9 code)	Age, sex, anxiety disorders, mood disorders, alcohol-related disorders, diabetes, dyslipidemia, hypertension and its complications, (including depression and anxiety), cerebrovascular disorders	*Cumul dose (Number of Defined Daily Dose, DDD):* . 90 to 180 DDD *versus* < 90 DDD: OR=1.28 (0.97-1.68); 1.07 (0.80-1.42)* . > 180 DDD *versus* < 90 DDD: OR=1.39 (1.12-1.73); 1.32 (1.05-1.64)* *Cumul days:* . 90 to 180 days *versus* <90 days: OR=1.38 (1.03-1.83); 1.25 (0.93-1.67)* . >180 days *versus* <90 days: OR=1.45 (1.18-1.79); 1.43 (1.16-1.77)* *Chronic use:* >6 months *versus* ≤6 months use: OR=1.34 (1.09-1.64); 1.24 (1.01-1.53)*
National Health Insurance Research database study, Taiwan (Wu et *al.* 2011[8]) *Case-control study*	25,140 (≥45 years)	11 years	Dementia all types (ICD-9 code)	Age, sex, anxiety disorders, health care system utilization, mood disorders, alcohol related disorders, psychotic related disorders, substance use disorders, sleep disorders, diabetes, hypertension and its complication, cerebrovascular disorders, parkinsonism, epileptic disorders	*History of use in all users:* . current use (no discontinuation) *versus* non-use: OR=2.71 (2.46-2.99) . former use (<1 year discontinuation) *versus* non-use: OR=1.68 (1.52-1.86) . former use (1 to <2 years discontinuation) *versus* non-use: OR=1.23 (1.09-1.39) . former use (2 to <3 years discontinuation) *versus* non-use: OR=1.22 (1.06-1.40) . former use (≥3 years discontinuation) *versus* non-use: OR=1.08 (0.98-1.20) *History of use in light users (i.e., 1 to <90 Defined Daily Dose):* . current use (no discontinuation) *versus* non-use: OR=4.66 (3.99-5.45) . former use (<1 year discontinuation) *versus* non-use: OR=1.63 (1.44-1.84) . former use (1 to <2 years discontinuation) *versus* non-use: OR=1.06 (0.92-1.24) . former use (2 to <3 years discontinuation) *versus* non-use: OR=1.13 (0.96-1.33) . former use (≥3 years discontinuation) *versus* non-use: OR=1.03 (0.93-1.15) *History of use in medium users (i.e., 90 to <360 Defined Daily Dose):* . current use (no discontinuation) *versus* non-use: OR=3.06 (2.66-3.52) . former use (<1 year) *versus* non-use: OR=1.54 (1.33-1.78) . former use (1 to 2 years discontinuation) *versus* non-use: OR=1.34 (1.09-1.65) . former use (since 2 to <3 years) *versus* non-use: OR=1.26 (0.96-1.66) . former use (≥3 years) *versus* non-use: OR=1.15 (0.93-1.42) *History of use in heavy users (i.e., ≥360 Defined Daily Dose):* . current use *versus* non-use: OR=2.12 (1.89-2.38) . former use (<1 year) *versus* non-use: OR=1.87 (1.61-2.18) . former use (since 1 to 2 years) *versus* non-use: OR=1.73 (1.34-2.24) . former use (since 2-3 years) *versus* non-use: OR=1.67 (1.17-2.40) . former use (≥3 years) *versus* non-use: OR=1.65 (1.20-2.26)
Caerphilly prospective study, South Wales (Gallacher *et al.* 2011[9]) *Case-control or cohort study?*	1134 men (≥45 years)	22 years	Dementia all types (DSM-IV criteria), Non-vascular dementia (DSM-IV criteria), Vascular dementia (NINCDS-AIREN criteria)	Age, social class, smoking, alcohol intake, education, body mass index, angina, anxiety, cognitive function test (National Adult Reading Text, Mini-Mental State Examination, AH4, Choice Reaction Time, Cambridge Cognitive Examination), ischemic heart disease, distress, anxiety, daytime sleepiness	*Ever use versus never use:* OR=2.94 (1.16-7.46)†; OR=3.59 (1.04-12.36)‡ *Cumul duration versus never use:* . ≤4 years *versus* non-use: OR=4.38 (1.15-16.75)†; OR=6.61 (1.42-30.83)‡ . >4 years *versus* never use: OR=2.31 (0.74-7.20)†; OR=1.86 (0.31-10.96)‡ *History of use:* . former use *versus* never use: OR=2.64 (0.71-9.78)†; OR=4.19 (0.90-19.49)‡ . recent use *versus* never use: OR=2.44 (0.78-7.57)†; OR=2.03 (0.38-10.75)‡ . current use *versus* never use: OR=2.64 (0.64-10.97)†; OR=3.47 (0.61-19.85)‡

*Sensitivity analysis excluding benzodiazepine related drug; †All dementia; ‡Non-vascular dementia

3.2. Quality assessment of the studies

Next, we will briefly discuss the way the 6 studies fulfilled or not the Newcastle-Ottawa quality criteria, for prospective and retrospective studies, respectively. The studies by Wu *et al.*[5 8] and Lagnaoui *et al.*[6 7] were examined using the Newcastle-Ottawa criteria for case-control studies. The designs used by Fastbom *et al.*[10] and Gallacher *et al.*[9] studies were rather difficult to interpret. Indeed, in the abstract section, Fastbom et *al.*[10] described their study as a case-control comparison but as an exposed/non-exposed comparison in the method section. Gallacher *et al.*[9] presented their study as prospective but the methodology described is more in accordance with a retrospective analysis. Consequently, these two studies will be analysed using the Newcastle-Ottawa criteria for both prospective and retrospective studies. The results obtained will be compared and commented.

3.2.1. Case-control studies

3.2.1.1. Selection of cases and controls

For case definition, three of the six studies used a diagnosis based on DSM-III-R[143] and independently validated by an external senior practitioner (Fastbom *et al.*,[10] Lagnaoui *et al*. 2002 and 2009[6 7]). In Gallacher et *al.*[9] the diagnosis was made according to DSM-IV[144] for dementia and NINCDS-AIREN[15] for possible or probable vascular dementia. These diagnoses appear to be quite reliable even if no details were given about the conditions in which they were made. The two studies by Wu *et al.*[5 8] used the diagnoses (ICD-9 codes) recorded in a Health Insurance database, which is less satisfactory (robustness, delay in recording the diagnosis, etc.). Lagnaoui *et al.* 2009[6] combined dementia and CIND diagnoses in their case definition which could make representativeness questionable. In all the studies, the samples seemed to be adequately representative of their source population. Similarly, in all studies, controls were defined by the absence of history of dementia at the end point.

Some points not taken into account in the scoring process of the Newcastle-Ottawa scale, could have compromised the representativeness of the sample:

- Information concerning the representativeness of the sample at baseline was not provided, except for Lagnaoui *et al*.[7] who reported concordant results with one other study done in the same region over the same period of time both for case and control exposure. Non-response rate was seldom given, even when it was high (*e.g.* Fastbom *et*

al.,[10] 45%) and the characteristics of non-respondents at baseline were never mentioned. That could have led to a selection bias if the absence of response was linked with the probability of benzodiazepine exposure or with the risk of cognitive decline or dementia.

- The cases of dementia recorded in databases are likely to correspond to the most severe forms of the disease. In these conditions, the case identification process could convey selection bias.

- In the study by Gallacher *et al.*,[9] only subjects with a complete follow-up (22 years) were considered for analyses. Therefore, it is possible that the subgroup of long-term survivors differed from the source population with regard to the probability of exposure and outcome. The same remark could be made for Fastbom *et al.*,[10] even if the short duration of follow-up (3 years) made it less likely that the over-representation of long-term survivors impacted the results.

- In some studies, definition of controls was more restrictive and imposed the absence of a dementia diagnosis during the entire follow-up, even if recorded after having been matched at index date with a case. That may have led to another sort of survival bias and to the selection of "abnormally" healthy controls.

3.2.1.2. Comparability

While cases and controls were made comparable for variables such as age and gender in all studies, in several of the studies some putative confounders, *i.e.* strongly linked to benzodiazepine use[8 6] and dementia,[1 4 5] were not controlled for, such as educational level (Wu *et al.*[5 8]) and depressive symptoms (Lagnaoui *et al.* 2009[6] and Fastbom *et al.*[10]).

3.2.1.3. Ascertainment of exposure

Exposure was ascertained in all the studies in the same way, in both cases and controls. In three papers,[5 6 8] exposure was ascertained on the basis of information provided by Health Insurance databases, which cannot guarantee that medications purchased were actually used or used at the time recorded. Studies by Fastbom *et al.*[10] and Lagnaoui *et al.* 2002[7] both used exposure data ascertained by both face-to-face interviews and inspection of drug packages by persons who were blind to the study hypothesis. Gallacher *et al.*[9] did not provide any information about the way exposure data were collected. In Lagnaoui *et al.* 2009[6] and Gallacher *et al.*[9] the rate of missing data was provided without specifying whether it differed between cases and controls. In

Lagnaoui *et al.* 2002[7] the non-response rate for exposure was higher in cases, but it was not possible to know whether this difference (28% of missing values in cases *versus* 9% in controls in the "current"/ "former" use analysis) was able to alter the estimates. In Fastbom *et al.*[10] the non-response rate for exposure was not provided.

3.2.2. Cohort studies

3.2.2.1. Selection of exposure groups

In the studies by Fastbom *et al.*[10] and Gallacher *et al.*[9], the comparison group was drawn from the same population as the exposed group. In these studies, only subjects with a complete follow-up were considered for analyses. However, this choice, which was sensible for maximizing the follow-up duration, can convey a risk of selection and immortal time bias if missing values, *e.g.* survival or loss to follow-up, differed across exposed and unexposed groups. Indeed, the attrition rate was about 45% in the study by Fastbom *et al.*[10] but was not mentioned by Gallacher *et al.*[146] In Fastbom *et al.* study,[10] exposure assessment combined both face-to-face interviews and inspection of drug packages. Gallacher *et al.*[9] did not specify the collection method for exposure data. Nor did they attest that a clinical dementia was not present during the period in which exposure was researched. Indeed, the diagnosis as reported in the article seems to have been based on a single assessment at the end of the follow-up (*i.e.* in subjects who had survived 22 years after inclusion) and not before.

Moreover:

- In Fastbom et *al.*[10] the non-response rate and characteristics of non-respondents at baseline were not provided. This raises a concern about a selection bias if the probability of non- response was linked to the exposure status.

- In the two studies, subjects with missing values for exposure were excluded without having their comparative characteristics provided. This could have made the representativeness of exposed or non-exposed groups questionable if exclusion due to missing information was linked in some way with the exposure status.

3.2.2.2. Comparability

Both studies controlled for the major confounders and obviously for age and gender. In the study by Fastbom *et al.*,[10] depressive disorders were not taken into account, although they are known to be strongly linked to both benzodiazepine use[86] and dementia.[145]

3.2.2.3. Outcome

In the study by Fastbom *et al.,*[10] the dementia diagnosis was based on DSM-III-R,[143] and validated by a senior neurologist not aware of the study hypothesis. In Gallacher et *al.*[9] this diagnosis was made according to the DSM-IV[144] criteria for dementia and NINCDS-AIREN[15] criteria for possible or probable vascular dementia and appeared to be quite reliable.

3.2.2.4. Follow-up duration

For Fastbom *et al.*[10] the subjects were followed over a period that was possibly too short to observe a delayed outcome and to control for confounding and reverse causation, owing to the long latency of the disease. Indeed, as benzodiazepine use is often chronic in the elderly, it is likely that a significant number of prevalent users initiated their treatment many years before the dementia diagnosis, possibly because of prodromal symptoms.

Table 11 summarises the quality assessment for the six studies. More details on the quality criteria and the attribution of the corresponding stars are available in Annexes 4.

Table 11. Quality of the studies evaluated using the Newcastle-Ottawa Scale

Case-control studies	**Selection** (maximum 4 ★)	**Comparability** (maximum 2 ★)	**Exposure** (maximum 3 ★)	**Total ★** (maximum 9 ★)
Fastbom *et al.* 1998[10]	★★★★	★	★★	7
Lagnaoui *et al.* 2002[7]	★★★★	★★	★★	8
Lagnaoui *et al.* 2009[6]	★★★	★	★	5
Wu *et al.* 2009[5]	★★★	★	★★	6
Wu *et al.* 2011[8]	★★★	★	★★	6
Gallacher *et al.* 2011[9]	★★★	★★	★	6
Cohort studies	**Selection** (maximum 4 ★)	**Comparability** (maximum 2 ★)	**Outcome** (maximum 3 ★)	**Total ★** (maximum 9 ★)
Fastbom *et al.* 1998[10]	★★★★	★	★	6
Gallacher *et al.* 2011[9]	★★	★★	★★	6

The better quality score of the Fastbom *et al.*[10] study when evaluated using the Newcastle-Ottawa criteria for case-control studies is in part explained by the fact that the scale does not consider whether the follow-up duration is sufficient or not to properly evaluate the association between exposure and outcome.

4. Discussion

We propose to provide an answer to the three main questions constituting the objective of the present review (see 1.2):

- Do the conclusions of these studies converge towards an overall answer regarding the link between benzodiazepine use and dementia? (cf. Congruence of the results: subsection 4.1).
- Does this overall answer, if any, seem valid? (cf. Validity of the results: subsection 4.2).
- Are there opportunities for new studies (unsolved questions, identified limitations justifying the development of new approaches to improve our knowledge on the relationship between benzodiazepine use and dementia)? (cf. Opportunities for new studies: subsection 4.3).

4.1. Congruence of the results

4.1.1. Direction of the results and homogeneity

Out of the six studies identified four,[5 7-9] concluded that there was a statistically increased risk. In one study,[6] the increased risk was not statistically significant owing to insufficient sample size. The earliest study[10] concluded that there was a paradoxical protective association; this was probably related to misclassification of exposure (past-users of benzodiazepines being included in the reference group).

4.1.2. Strength of association and variability

The strength of association ranged from 1.24 to 4.38 for the studies having reported a statistically significant increase in the risk of dementia in benzodiazepine users. These differences could be explained by the various definitions retained for exposure (*e.g.* recent

initiation, past use, current use, chronic use etc.) selecting various patterns of use which could correspond to different risks of dementia. For example, in the Wu *et al.* studies[5 8] it was not surprising to observe an absence of excess risk in users of less than 3 cumulative months (note: in their study conducted in 2009, this group was pooled with non-users as the reference group) and a risk that increased with cumulative dose or duration of exposure. The same authors reported a reversibility of the association 1 to 2 years after discontinuing the treatment in light users (<90 DDDs) but not in heavy users (>360 DDDs during follow-up), even 3 years or more after discontinuation (OR 1.64; 95%CI 1.20-2.26). Among the *ever users* of benzodiazepines with an increased risk of dementia, Lagnaoui *et al.* 2002[7] attributed the association to past-users while the study by Gallacher *et al.*[9] had a too small sample size and too low statistical power to research the strength of the association for different patterns of exposure such as chronic or not, past or recent, etc.

4.2. Validity of the results

The Newcastle-Ottawa criteria evaluate the plausibility of the three main causes of analytic bias in observational studies: selection bias, confusion bias and information bias. Other types of bias (mainly protopathic bias) are not specifically assessed by the scale, despite having a major influence on the internal validity of the studies considered.

We finally used two different approaches to score confidence in the conclusions of the studies: (i) the Newcastle-Ottawa criteria (studies with a score of 5 stars or less were considered as non-robust), (ii) the plausibility of a protopathic bias since not specifically assessed by the Newcastle-Ottawa criteria. As summarised in Table 6, three levels of confidence combining these two assessments were used: *low confidence* (low quality according to Newcastle-Ottawa criteria or good quality but protopathic bias considered as likely), *average confidence* (good quality but protopathic bias considered as possible), *good confidence* (good quality and results unlikely to be explained by a protopathic bias). Considering both the quality score as evaluated by the Newcastle-Ottawa scale and the likelihood of a protopathic bias as a possible explanation for the results, confidence in the conclusions provided by three of the studies[6 9 10] was considered as "low" and for the other three[5 7 8] it was considered as "average". (Table 12).

Table 12. Confidence in the results of studies assessing the relation between benzodiazepine use and dementia

Study	Dementia risk in benzodiazepine users	Newcastle-Ottawa scale, total ⋆ (maximum quality: 9⋆)	Protopathic bias explaining the results	Confidence in the results
Fastbom *et al.*, 1998[10]	Decreased	6 (cohort study) 7 (case-control study)	likely (because of short follow-up)	low
Lagnaoui *et al.*, 2002[7]	Increased	8 (case-control study)	likely (for ever use and current use estimations) possible (for former use ≥3 year discontinuation)	low average
Lagnaoui *et al.*, 2009[6]	Increased (not significantly)	5 (case-control study)	likely (because of short follow-up)	low
Wu *et al.*, 2009[5]	Increased	6 (case-control study)	likely (in main analysis, time of exposure not taken into account) possible (in sensitivity analysis excluding hypnotics)	low average
Wu *et al.*, 2011[8]	Increased	6 (case-control study)	likely (in analysis considering current use and former use <3 year discontinuation) possible (in former users ≥3 year discontinuation)	low average
Gallacher *et al.*, 2011[9]	Increased	6 (case-control study) 6 (cohort study)	likely (in analyses based on ever users, other analyses inconclusive)*	low

*Note: subgroup analysis discriminating recent initiators (likely to convey a protopathic bias) and past initiators (unlikely to convey a protopathic bias) were inconclusive because of low sample sizes.

4.3. Opportunities for new studies

None of the five studies that had concluded there was an association between benzodiazepine use and dementia achieved results with a high level of confidence. Consequently, the nature of this association, causal or not, remains unclear:

- On the one hand, because of a unsatisfactory controlling for a possible reversed causality or protopathic bias owing to (i) an insufficient duration of follow-up, given the very long latency period of the disease,[6 7] (ii) an exposure definition not adequately taking into account the delay between exposure start and the diagnosis of dementia (recent initiation or initiation in the past),[5-8] (iii) a lack of statistical power to adequately take into account these different periods of exposure.[9] Indeed, treatments started a few years before the diagnosis might not be the cause of the disease but motivated by some of its prodromes.

- On the other hand, because of the lack of valid information about a possible dose-effect relationship, which would be a compelling argument for drug causation.

These conclusions opened opportunities for new studies attempting to circumvent these two types of limitation.

5. Summary

- Among the six studies identified as covering the topic, five were in favour of an increased risk of dementia in benzodiazepine users.

- Those studies suffered from methodological limitations, in particular unsatisfactory controlling for a possible reverse causality or protopathic bias.

- The nature of the link, whether causal or not, between benzodiazepines and dementia, as reported by the five studies, remains unsolved. This gives an opportunity for new studies taking into account the previous limitations.

PART III – The BENZODEM programme (PAQUID cohort)

1. Context and objective

1.1. The context in a few questions

WHAT DO WE KNOW?

Five observational studies[5-10] had previously put forward an increased risk of dementia in benzodiazepine users. However the nature of this association, causal or not, remained unclear mainly because of:

- A follow-up duration that was often too short given the very long latency period of dementia (cf. Part II).

- Unsatisfactory controlling for a possible reversed causality or protopathic bias. Indeed treatments initiated a few years before the diagnosis might be suspected of not being the cause of the disease but simply of being motivated by some of its prodromes (cf. Part II).

WHAT DO WE NOT KNOW?

Since the studies previously conducted did not succeed in providing valid answers to these criticisms, exploring this association further remained of major interest. Indeed:

- An association proven to be causal, at least in part, would result in tremendous consequences regarding the number of the cases in excess since the prevalence of benzodiazepine use and dementia are both high in the elderly population (cf. Part I).

- As treatment options for the various types of dementia remain particularly limited, identifying alterable factors modifying the probability of dementia is crucial. It is possible that benzodiazepine use is one of these. Indeed, (i) their main pharmacological properties rely upon an inhibitory effect at the level of the central nervous system, and (ii) they are known to induce, in some circumstances, short-term amnesia or confusion (cf. Part I).

- Finally, if benzodiazepines were found to have a causal role, intervention plans aiming to minimise the risks induced would be relatively straightforward to implement.

1.2. Objective

The BENZODEM programme aimed to assess the association between benzodiazepine use and the subsequent risk of dementia with special attention paid to minimising the influence of a protopathic bias on the results.

2. Study population: the PAQUID cohort

2.1. Presentation

PAQUID (Personnes âgées QUID?) is a prospective French cohort aiming to study normal and pathological brain ageing. In 1988-89, this programme included, a sample of 3777 individuals, aged 65 years and older, randomly extracted from electoral lists of Dordogne and Gironde, two administrative areas (departments) of South-Western France. Participants have been shown to be representative of the non-institutionalized elderly general population of this geographical area. A large amount of socio-demographic and medical data are collected periodically (every 2-3 years) and the follow-up currently accounts for more than 25 years. This follow-up is still ongoing and data from 9 transversal follow-ups (inclusion and then 3, 5, 8, 10, 13, 15, 17 and 20 years after) were available for our analyses. Data were collected during face-to-face interviews conducted at the patient's home by trained neuropsychiatrists using standardized questionnaires. Socio-demographic, life conditions and habits, functional abilities, health conditions, cognition were evaluated at each time point. Medicine use was evaluated from self-administered questionnaires and was validated by inspection of drug packages. Dementia was scrutinized at each time point by neuropsychiatrists on the basis of the DSM-III-R criteria[143] and, when appropriate, validated by a senior neurologist using the NINCDS-ADRDA criteria[13] for dementia. The design and method of the PAQUID programme have been described in detail elsewhere.[147] The number of participants at each follow-up date is provided in Table 13.

Table 13. Number of participants at each follow-up date of the PAQUID study who were available for the BENZODEM programme

PAQUID	T_0	T_1	T_3	T_5	T_8	T_{10}	T_{13}	T_{15}	T_{17}	T_{20}
Date	1988-90	1989-90	1991-93	1993-95	1996-97	1998-00	2001-02	2003-04	2005-06	2008-09
Seen	3777	1850	2315	2084	1566	1461	1041	832	682	505
Cumul. deaths	-	108	472	848	1273	1552	2076	2429	2738	3014

2.2. Advantages of the PAQUID cohort

For the BENZODEM programme, the main advantages of using the PAQUID cohort were:

- Its long follow-up (>20 years), an exceptional feature for a cohort study focusing on the elderly population,
- The robustness of the diagnoses of dementia,
- The validity of the ascertainment of exposure at each following point,
- The vast amount of variables recorded, providing numerous possibilities for adjustments.

Dementia is characterized by a long latency period, the duration of which is not precisely known but thought to be at least 10 years and probably markedly more.[19] During this period, prodromal manifestations may be observed. Interestingly, some of them (depression, anxiety, insomnia) correspond to the main reasons for benzodiazepine prescription. The time distribution of these prodromes is not precisely known but it is sensible to consider that their highest prevalence falls into the 5-year period before dementia.[29 139 140] This point represents the main criticism levelled against the statement referring to an increased risk of dementia in benzodiazepine users made by previous studies. Indeed, for most of them, the duration of follow-up was rather short and the reported association was possibly spurious *i.e.* created artificially by the fact that benzodiazepines were not the cause of the disease but in fact prescribed for symptoms related to its early manifestations, such as depression, anxiety or insomnia. This fallacy enters into the framework of reverse causality or protopathic bias.

The long follow-up in the PAQUID study (20 years) allowed us to take into account a large proportion of the disease's long latency period and thus minimise as far as possible the influence of a putative protopathic bias when researching a causal relationship between benzodiazepine use and dementia.

2.3. Limitations of the PAQUID cohort

Despite its huge benefits, the PAQUID programme did have some inherent limitations in the context of our research objective:

- The follow-up is based on face-to-face interviews conducted every 2 or 3 years. Therefore, there is no information about drug exposure, onset of an event or other variables for the period comprised between two measurements.

- The measurement of drug exposure suffers some other limitations. First, information about the dose is not available in the PAQUID programme. It is thus impossible to research a dose-effect relationship, which is a valuable argument for drug causation. Moreover, because of the cross-sectional nature of the exposure assessment, exploring the effect of the duration of exposure implies an *a priori* hypothesis: an exposure declared at two subsequent dates corresponds to an exposure maintained between these two dates, and also an absence of exposure at two subsequent dates indicates a non-exposed period. If we are considering the frequently chronic nature of benzodiazepine use in the elderly population,[131 148] these assumptions are not unrealistic although they do not reflect the reality in some circumstances *e.g.* intermittent use, short-term use, etc.
- PAQUID is a fixed cohort, *i.e.* without new inclusions or replacements over time. Therefore, a large proportion of participants died or were lost to follow-up before the 10th year of follow-up, the minimum delay required to validly explore the prodromal phase of dementia (Table 13).

3. Prospective approaches

3.1. Presentation

3.1.1. Choice of the best adapted design

After having compared the pros and cons of the various methodological options, the choice made for the main analysis was clearly for a prospective approach, which was preferred over a retrospective design for several reasons:

- In essence, a cohort design comparing the incidence rates between exposed and non-exposed provides incidence rate ratios directly, and these are a more satisfactory estimate than odds ratios, particularly when the frequency of the disease is expected to be high during the study period (>10%), which was typically the case for dementia.
- A cohort study, if properly designed, enables us to be more confident, at least theoretically, about the fact that exposure preceded the disease and, for that reason, generally provides a higher level of proof than a case-control study when ascertaining a causal relationship.

- Overall, the cohort design enables us to describe the distribution of the onset delays of the cases of the disease in each group, exposed or not, which is valuable information when assessing the plausibility of a protopathic bias.
- Finally, another argument was that most of the studies conducted so far were of the case-control type.

In the present case, designing a cohort study appeared to be feasible since:

- The incidence of the outcome, *i.e.* dementia, was expected to be high enough during the PAQUID follow-up.
- The long follow-up, *i.e.* 20 years, enables us to take into account, at least in part, the latency period of the disease.
- Data had already been collected and recorded and made available for our research team for developing an historical design without additional costs.

However, the expected variability of the exposure patterns made the design and the exposure definition rather complex. Indeed, they should ideally take into account:

- The time lag after exposure start, making a person prone to develop a dementia caused, at least in part, by exposure. Making assumptions about this delay would have required knowledge about (i) the average extent of the latency period of a dementia, whatever its type, (ii) the mechanism by which exposure could increase the baseline risk of dementia.
- The variability of exposure patterns over the follow-up period *e.g.* recent, past, short-term, long-term, periodic, and its influence on the above process.

3.1.2. General questions and hypotheses

The BENZODEM cohort approach consisted of two prospective studies taking advantage of the 20 years of the PAQUID follow-up. In analysing the existing literature and keeping in mind that benzodiazepines can impair memory and cognition, it is not unlikely that a higher risk of dementia may be observed among users of these drugs. However, our questioning was about the reality of this excess risk if it were not for the most part explained by a methodological fallacy such as a protopathic bias. Before designing the research protocol, two assumptions were made:

- First, in the event of an association explained by a protopathic bias, the excess risk would be mainly observed during the (few) years following exposure start. Indeed, even if the

latency period of the disease is quite long, *i.e.* at least 10 years and possibly 20 or 30, the time distribution of its prodromes is expected not to be constant over time: their incidence is assumed to increase when the pathological process becomes more advanced, *i.e.* when moving toward the date of the clinical diagnosis.

- For the same reason, an excess risk, if any, should be researched long after exposure initiation.

3.2. Main approach

3.2.1. Method

3.2.1.1. Observation period

A "run-in" period was maintained before the actual start of the follow-up, which was considered as the index date for analyses and fixed at T_5, *i.e.* the fifth year after inclusion in the PAQUID cohort. The purpose of this run-in period was:

- To exclude prevalent users of benzodiazepines, *i.e.* subjects found exposed at T_5 and/or before this date (T_3 and T_0 or T_3 or T_0). Indeed, our main design option was to restrict the analyses to new initiators since for prevalent users the date of the actual exposure start, which was possibly much earlier, remained uncertain. This therefore, (i) made controlling for confounding and protopathic biases a complex matter, (ii) precluded the possibility of analysing the delay between exposure start and the onset of dementia, and, above all, (iii) conveyed a risk of depletion of susceptibles or survivor bias: those who were still being treated at inclusion time were likely to have presented the least adverse effects, particularly for cognitive functions and to have the least chance of developing a dementia. Including these subjects could tend to underestimate the strength of the association and even lead to a paradoxical but spurious protective effect of benzodiazepines.
- To ascertain that the follow-up actually enrolled dementia-free subjects after having excluded those with a diagnosis of dementia recorded at T_0, T_3 or T_5.
- To obtain information about the level of cognitive functions of all participating subjects, assessed by different tests, before starting the follow-up. That allowed adjustment on this parameter for neutralizing putative differences across groups before exposure started.

Starting the follow-up at T_5 and not T_3 was necessary to ensure at least three years of observation for each subject before inclusion in the study. Indeed, moving the index date back to T_3 would have made it possible to include subjects exposed to benzodiazepines for almost 3 years, *i.e.* those not exposed at T_0 but who started their treatment just after this date. Restricting analyses to subjects not exposed at T_0 and T_3 for the exposed group and not exposed at T_0, T_3 and T_5 for the control group made this scenario unlikely and reinforced the validity of the "new-user" definition. These points are developed in the Discussion section (cf. subsection 6.1.3, comments 6 and 7).
On the other hand, starting the study at T_5 and not at T_0 or T_3 resulted in (i) greatly reducing the sample size and, consequently, the statistical power, and (ii) shortening by 5 years the follow-up available for analyses.

3.2.1.2. Eligibility criteria

People were eligible to participate if (i) they were still being followed at T_5 with no missing values for exposure or dementia at T_0, T_3 and T_5, (ii) they were not diagnosed with dementia at T_0, T_3 or T_5, and (iii) they did not declare prevalent use of benzodiazepines at T_0 or T_3.

3.2.1.3. Exposed groups

Data on drug use, including benzodiazepine use, were collected with a standardised questionnaire at each follow-up visit. In addition, participants or their usual caregivers were asked about prescribed and non-prescribed drugs used regularly during the previous two weeks. The interviewer then validated drug use by visual inspection of the participant's medicine packs. As the study was conducted by using historically collected and recorded data, neuropsychologists who carried out the face-to-face interviews were unaware of the hypothesis of our study.

We classified all eligible participants as new benzodiazepine users or non-users according to ascertainment of exposure at T_5 (Figure III). The exposed group was made up of participants without declared benzodiazepine use at T_0 and T_3 and a first declaration at T_5. Participants without any declared use at T_0, T_3 and T_5 were considered as non-users and served as the reference group. We did not consider exposure after T_5 in the main prospective analysis study but in a second prospective approach described in subsection 3.3.

We considered all benzodiazepines and related drugs available in France since 1988 (alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, clotiazepam, diazepam, estazolam, flunitrazepam, loflazepate, lorazepam, loprazolam, lormetazepam, nitrazepam, nordazepam, prazepam, oxazepam, temazepam, tetrazepam, tofizopam, triazolam, zolpidem and zopiclone).

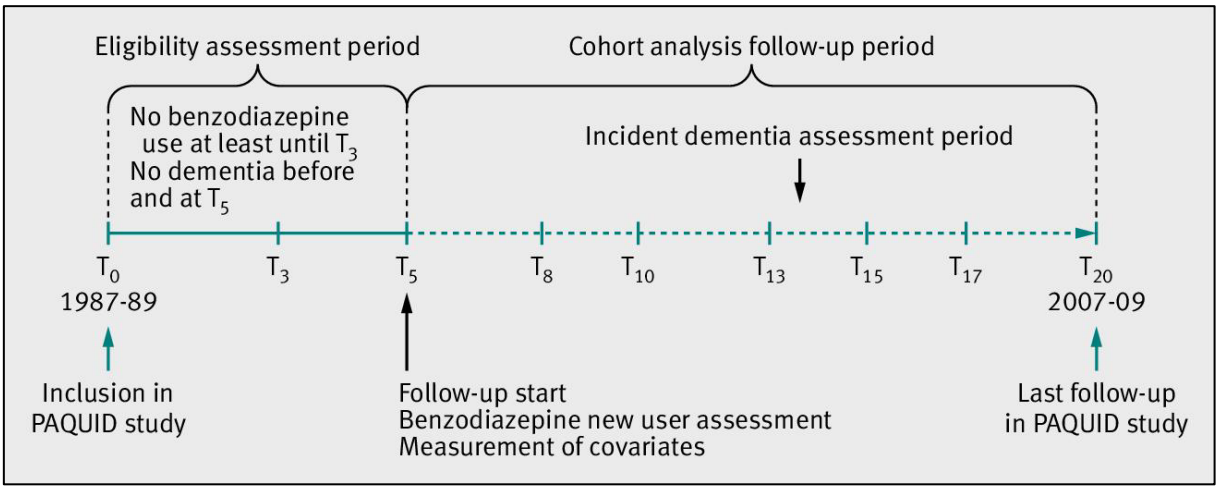


Figure III. Follow-up scheme and study design for primary cohort analysis (Billioti de Gage *et al.*[149])

3.2.1.4. Outcome

At each follow-up date, trained psychologists systematically assessed dementia on the basis of the DSM-III-R criteria.[143] A senior neurologist further examined all suspected cases to confirm or not the diagnosis of dementia. Our main outcome was dementia of all types. As follow-up visits took place every two or three years, we assigned the midpoint of the time interval between two follow-up visits as the date of the dementia diagnosis. For example, for a diagnosis of dementia recorded at T_{10} and not present at T_8, the dementia was assumed to have occurred in the ninth year of follow-up for the PAQUID cohort and therefore the fourth year for our analyses. Incident cases of dementia were identified using information from the six visits (T_8, T_{10}, T_{13}, T_{15}, T_{17} and T_{20}) during the entire follow-up period available for analyses, *i.e.* 15 years. (Figure III).

3.2.1.5. Adjustment

3.2.1.5.1. Main confounders

The main variables suspected to have a likely association with both benzodiazepine exposure and dementia risk were included in the adjustment model.[86 117 150 151] These factors were: age (70-79, 80-84 or ≥85 years), gender, education level (<7 or ≥7 years), marital status (single or not), regular wine consumption and cardiovascular background identified by the use of antihypertensives, antidiabetics, statins, platelet inhibitors or oral anticoagulants as proxies. Theses factors were measured at the study index date (T_5). In case of missing values, estimations were made using the declaration at T_3 or T_0. The particular case of neuropsychiatric symptoms is discussed below, mainly in subsection 3.2.1.5.3.

3.2.1.5.2. Cognitive decline

Cognitive decline before the index date (T_5) was considered, with the aim of identifying individuals more at risk of developing dementia or being already in a neurodegenerative process preceding the clinical onset of a dementia. These persons were particularly prone to presenting prodromal symptoms, such as anxiety, sleep disorders or depression, justifying the prescription of benzodiazepines. Therefore, an adjustment on the level of cognitive decline before index date (T_5) would tend to minimise the influence of a putative protopathic bias on the estimates. Cognitive decline was assessed by changes between T_0 and T_3, in the scores of three tests exploring cognitive functions: the Mini-Mental State Examination (MMSE, evaluating general cognitive functioning),[152] the Benton Visual Retention Test (BVRT, evaluating visual memory)[153] and the Isaacs Set Test (IST, evaluating verbal fluency).[154] Cognitive decline is a better predictor of a neurodegenerative process than absolute scores at psychometric tests, where the interpretation may vary according to several factors such as age and education level particularly.[155]

3.2.1.5.3. Neuropsychiatric symptoms

A clear limitation of the PAQUID programme for the intended analyses was that the two main indications for prescribing benzodiazepines, *i.e.* anxiety and sleep disorders, were not specifically researched and recorded. Neuropsychiatric symptoms were explored as a whole at each follow-up date by means of the Center Epidemiologic Studies Depression scale (CES-D).[156]

Although this scale was developed to evaluate the presence and the severity of depressive disorders, some of its items concern anxiety and sleep disorders.
In any case, taking into account depressive disorders in the adjustment models is complex because:

(1) **The exact nature of the relationship between depressive disorders and dementia remains controversial.**[157]

Indeed, the presence of episodes of depression occurring before the clinical diagnosis of dementia could be considered, among other hypotheses, as:

- *A prodrome of the disease:*[63 64] Individuals could present a higher incidence of depressive disorders in the years preceding the clinical diagnosis of the disease. There is no agreement about what "the years" means. Some authors refer to a short preclinical phase, while others suggest 20 years or more.[29 158] This point was discussed above (see 3.1.2). Moreover, even if depression is not an indication *per se* for prescribing benzodiazepines, it is well known that these drugs are often coprescribed or prescribed in place of an antidepressant when the depression is not identified as the cause of insomnia or anxiety. Even if the second association, *i.e.* depression-benzodiazepines, is more established than the first, *i.e.* depression-dementia, we are typically in the framework of a protopathic bias, possibly leading to the erroneous conclusion that benzodiazepine use causes dementia when it is a consequence of this disease through its prodromes. This bias differs from the classical confounding bias by the fact that the chronological sequences are one-sided: (i) depressive symptoms always precede the dementia diagnosis, and (ii) benzodiazepine use never precedes depressive symptoms.
- *A risk factor of the disease:*[60 61] Some well-conducted studies have shown that persistent or recurrent episodes of depression in middle age could be associated with a further higher risk of dementia. Here, the neuropsychiatric symptoms are not *per se* a prodrome but may be the early expression of a susceptibility associated both with a higher risk of neuropsychiatric disorders and dementia.

The difference between these two possible types of association may appear specious but it is of major importance for statistical analyses.

Consequently, taking into account depressive disorders when performing the statistical analyses was not an easy task for at least three main reasons:

- In a way, adjusting on depressive disorders could result in adjusting on the outcome (dementia) if these symptoms actually were prodromes of the disease. This could lead to a risk of overadjustment, thus minimising the chances of identifying an association, if any.
- Depressive disorders are only one type of neuropsychiatric symptom possibly involved in a confounding or a prothopatic bias. As mentioned above, other reasons for prescribing benzodiazepines, such as anxiety or insomnia, are not explored individually in the PAQUID study but are included "as a whole" in the CES-D scale. Therefore, they cannot be taken into account independently for an optimal control for protopathic bias.
- Even in the absence of protopathic or confusion bias, benzodiazepine prescription should always, at least in an ideal world, be concomitant with or subsequent to neuropsychiatric symptoms (anxiety, insomnia or depressive disorders) and recorded as such in the database. Therefore, adjusting on these symptoms would tend to make the exposed and control groups comparable in that respect and consequently restrict analysis of the effect of exposure on patients using benzodiazepines with no previously identified symptoms.

None of the methodological options, *i.e.* including or not depressive disorders in the adjustment models, appeared to be entirely satisfactory. Indisputably, not adjusting on depressive disorders certainly would have been subject to criticisms and probably unacceptable for the reviewers after submitting the article for publication. Therefore, a supplementary adjustment on depressive disorders was considered in a sensitivity analysis.

(2) **A choice to make for the marker of depressive symptomatology.**

There were two possibilities for identifying depressive disorders in the PAQUID cohort: an "abnormal" score from the CES-D scale or a recorded consumption of antidepressants. The CES-D scale is a straightforward self-administered questionnaire designed to identify and quantify depressive disorders in the general population. It is considered to be a useful and reliable tool for epidemiologic studies on depression.[159] Cut-off scores of ≥17 for men and ≥23 for women, as validated for the French population, indicate the existence of significant depressive symptoms.[156]

Even if it is not perfect, the CES-D scale appeared preferable to using antidepressants since, in France at least, congruence between the population presenting with depressive symptoms (the target population) and the population actually treated with antidepressants (joint population) is particularly low.[160] [161] Moreover, a significant proportion of patients with depressive disorders receive benzodiazepines and not antidepressants. As an example, Table 14 highlights the poor congruence between patients with depressive symptoms according to the CES-D scale and the use of antidepressants at inclusion in the PAQUID cohort: 40% of individuals identified as depressed by the CES-D scale were apparently not treated, less than 5% of them were treated with antidepressants without coprescription of a benzodiazepine, a large proportion of apparently depressed subjects (45%) received benzodiazepines without antidepressants, and 10% were treated with an association of antidepressants and benzodiazepines.

Table 14. Congruence between depressive symptoms, antidepressant (AD) or benzodiazepine (BZD) use at inclusion (T_0) in the PAQUID study (118 missing values for CES-D at T_0)

	Depressive symptoms (CES-D)		Total, n (%)
	Yes, n (%)	No, n (%)	
Antidepressants only	23 (4.6)	37 (1.2)	60 (1.6)
ADs+ BZDs	49 (9.7)	81 (2.6)	130 (3.6)
BZDs only	228 (45.1)	814 (25.8)	1042 (28.5)
No ADs and no BZDs	206 (40.7)	2121 (70.4)	2427 (66.3)
Total, n (%)	506 (13.8)	3153 (86.2)	3659 (100)

CES-D=Center for Epidemiologic Studies Depression scale; ADs=Antidepressants; BZDs=Benzodiazepines

3.2.1.6. Statistical analysis

We compared the characteristics of benzodiazepine new initiators with those of non-users using numbers and percentages for qualitative variables and median and interquartile range for quantitative variables.

We conducted a survival analysis using the remaining 15 years of follow-up available in the PAQUID programme (after the 5-year observation period described in 3.2.1.1). The aim was to compare “new initiators” of benzodiazepines to “non-users” with respect to the incidence of dementia over the entire follow-up (15 years). New initiators were subjects not treated with benzodiazepines at T_0 and T_3 but who started exposure at T_5 (index date). In fact, it was sensible to consider that the treatment was started somewhere between T_3 (no treatment recorded at

this date) and T_5 (first recording of exposure). The non-users were subjects not exposed at T_0, T_3 and T_5. Both groups were compared for:

- *Subsequent risk of dementia.* We used multivariable Cox Hazard Models adjusted for potential confounding factors measured at index date and described earlier (age, gender, education level, marital status, regular wine consumption, use of antihypertensive drugs, antidiabetic agents, statins, platelet inhibitors or oral anticoagulants) as well as for cognitive decline evaluated by the difference in the MMSE, Benton's or Isaac's tests scores between T_0 and T_3. As discussed above, depressive disorders could be considered as a potential prodromal symptom of dementia and, consequently, as an early manifestation of the disease,[64] [162] we therefore did not consider them in our main adjustment model (risk of overadjustment). However, this adjustment was made in a sensitivity analysis (after researching a potential interaction when evaluating the association) since depression has also been described as a risk factor for dementia.[60] [61] [163] The total person-times were computed from the index date (T_5, in the PAQUID follow-up) to the estimated date of dementia (see 3.2.1.4), death, loss to follow-up or the last measurement available in PAQUID (T_{20}), whichever came first. We researched whether the association between benzodiazepines and dementia was altered by age, gender or schooling duration.
- *Delay in dementia onset since index date.* We used Kaplan-Meier curves and the Log-Rank test for univariate dementia-free survival analyses in exposed and non-exposed. When an excess risk of dementia was observed in new initiators of benzodiazepines we assumed (see 3.1.2) that:
    - An excess risk observed only in the few years following the index date, *i.e.* short delay between exposure start and the diagnosis of dementia, would evoke an association which was for the most part explained by a protopathic bias.
    - Conversely, a significant association between dementia and exposure that started long before (>5 or 10 years) would make a protopathic bias less likely.

3.2.2. Results

3.2.2.1. Population selection

The selection process is summarised in Figure IV. Of the 3777 participants in the PAQUID study, 1063 were free of dementia at initiation of the study and without prevalent use of benzodiazepines at T_0 and T_3.

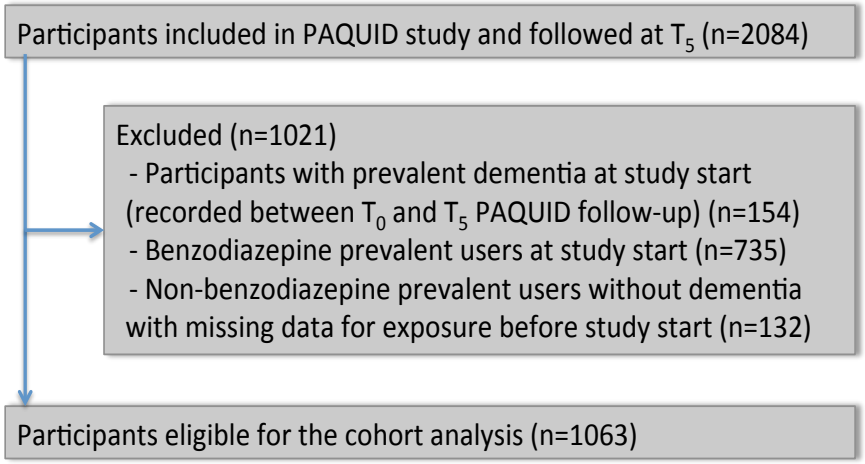


Figure IV. Identification of participants in the PAQUID programme still followed at T_5 and eligible for the main cohort analysis (no dementia and no prevalent benzodiazepine use), (Billioti de Gage *et al.*[149])

3.2.2.2. Exposed and non-exposed

The characteristics of participants included in the analysis according to benzodiazepine exposure status are presented in Table 15. Compared with non-users (n=968), new initiators of benzodiazepines (n=95) were more likely to have a shorter schooling duration (66% *versus* 77% with duration ≥7 years), to be single or widowed (52% *versus* 41%), to have more significant depressive symptoms (16% *versus* 4%), to use antihypertensive drugs (74% *versus* 58%), to use platelet inhibitors or oral anticoagulants (15% *versus* 6%) and to consume wine less regularly (63% *versus* 73%). No difference was found regarding age, gender, use of antidiabetic agents, use of statins, and cognitive evolution between inclusion in the PAQUID study (T_0) and the three year follow-up visit (T_3).

Table 15. Baseline characteristics of participants in the PAQUID programme included in the cohort analysis, according to benzodiazepine use. Values are numbers (percentages) unless stated otherwise (Billioti de Gage *et al.*[149])

Characteristics	Benzodiazepine new users (n=95)	Benzodiazepine non-users (n=968)
Median (interquartile range) follow-up (years)	6.1 (2.2-10.4)	6.2 (2.6-12.5)
Dementia*	30 (32)	223 (23.0)
Female sex	54 (57)	474 (49.0)
Age (years):		
70-79	35 (37)	385 (39.8)
80-84	26 (27)	240 (24.8)
≥85	34 (36)	343 (35.4)
Schooling duration ≥7 years	63 (66)	745 (77.0)
Single or widowed	49 (52)	394 (40.7)
Wine consumption	57/90 (63)	680/932 (73.0)
Significant depressive symptoms†	15/93 (16)	38/944 (4.0)
High blood pressure‡	70 (74)	562 (58.1)
Diabetes mellitus§	7 (7)	81 (8.4)
Statin use	5 (5)	36 (3.7)
Platelet inhibitor or oral anticoagulant use	14 (15)	55 (5.7)
Median (interquartile range) cognitive evolution trend:		
MMSE score difference between T_3 and T_0	0 (-1; 1)	0 (-1; 1)
Isaacs score difference between T_3 and T_0	0 (-2; 3)	0 (-3; 3)
Benton score difference between T_3 and T_0	0 (-2; 1)	0 (-1; 2)

MMSE=Mini-Mental State Examination.

*According to *Diagnostic and Statistical Manual of Mental Disorders*, third Edition, revised criteria.

†Based on Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women).

‡According to the use of antihypertensive drugs.

§According to the use of antidiabetic agents.

3.2.2.3. Association between benzodiazepine use and dementia

During the 15-year follow-up (median 6.2 years; interquartile range 2.6 to 12.3), 253 (23.8%) cases of dementia were confirmed, 30 (31.6%) in benzodiazepine initiators and 223 (23.0%) in non-users. New use of benzodiazepines between T_3 and T_5 was associated with a shorter dementia-free survival compared to non-use and with a significantly increased risk of dementia (Hazard ratio, HR 1.60, 95% confidence interval, 95%CI 1.08 to 2.38). Further adjustment on depressive symptoms and use of the Isaac or Benton's test instead of the Mini-Mental State Examination led to similar results. (Table 16).

Table 16. Association between new-use of benzodiazepines and incident dementia in the PAQUID study. Values are numbers (percentages) unless stated otherwise (Billioti de Gage *et al.*[149])

	Incident dementia	No dementia during follow-up	Hazard ratio (95%CI)
Analysis adjusted for age:*	**n=253 (%)**	**n=810 (%)**	
Benzodiazepine non-users	223 (88)	745 (92.0)	1.00 (reference)
Benzodiazepine new initiators	30 (12)	65 (8.0)	1.59 (1.09 to 2.34)
Main analysis:†	**n=240 (%)**	**n=766 (%)**	
Benzodiazepine non-users	211 (88)	708 (92.4)	1.00 (reference)
Benzodiazepine new initiators	29 (12)	58 (7.6)	1.60 (1.08 to 2.38)
Complementary analysis:†‡	**n=231 (%)**	**n=752 (%)**	
Benzodiazepine non-users	203 (88)	695 (92.4)	1.00 (reference)
Benzodiazepine new initiators	28 (12)	57 (7.6)	1.62 (1.08 to 2.43)

*At baseline (T_5).
†Adjusted for age, gender, schooling duration, singleness, wine consumption, use of antihypertensive drugs, use of antidiabetic agents, use of statins, use of platelet inhibitors or oral anticoagulants, and Mini-Mental State Examination evolution between inclusion (T_0) ant three year follow-up visit (T_3).
‡Adjusted for significant depressive symptoms according Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women) at baseline (T_5).

3.2.2.4. Incidence curves

The increased risk of dementia in new users of benzodiazepines compared to non-users appeared delayed (by 5 to 7 years) after initiation of benzodiazepine use (index date T_5). (Figure V).

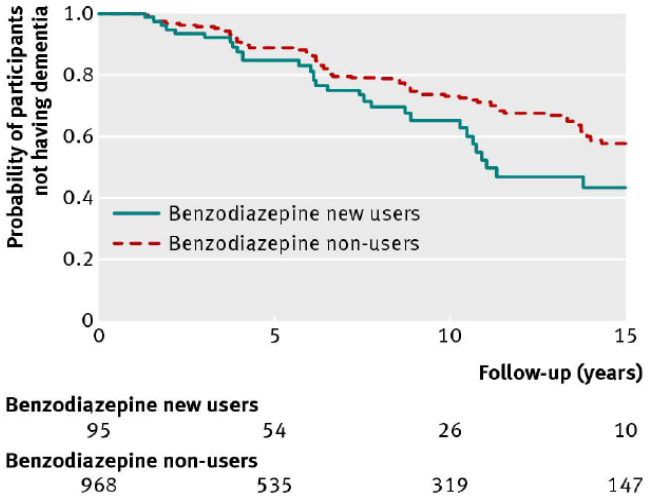


Figure V. Dementia-free survival in the PAQUID study in new users of benzodiazepines and non-users at baseline (T_5) (Billioti de Gage *et al.*[149])

3.2.3. Conclusion of the main prospective approach

This prospective approach, *i.e.* the main analysis of the BENZODEM programme, highlighted an increased risk of dementia in benzodiazepine new users which appeared delayed after the first record of use. This 5- to 7-year delay does not support an association explained for the most part by a protopathic bias.

3.3. Second approach: estimation of time-varying exposure

3.3.1. Justification

In the main approach a considerable share of the non-exposed group started a treatment with benzodiazepines after the index date and became exposed. Similarly, some subjects in the *new users* group stopped their treatment after the index date and remained non-exposed during a significant part of the follow-up. The second approach was also a prospective design and aimed to measure the influence of these exposure changes on the results and also to assess the plausibility that a protopathic bias accounted for a significant part of the results from the first approach. Indeed, with making reference to the assumption made in 3.2.1.6, one would expect that in the case of an association explained by a protopathic bias, the hazard ratio would increase when the delay between exposure start and dementia diagnosis became shorter.
Such an approach has not been retained as the main analysis, since our objective was to characterize the delay between exposure start and a possible excess risk of dementia. This information was crucial for discussing the plausibility of a protopathic bias and required maintaining the maximum follow-up time. Exploring the association over a shorter period would run the risk of missing a large proportion of delayed cases.

3.3.2. Method and results

3.3.2.1. Classical method to take into account time-varying exposure

3.3.2.1.1. First attempt

In a first and simple attempt we considered current benzodiazepine exposure as a time-varying variable using a Cox proportional hazards regression. At each time of occurrence of the event (dementia), the case was compared with the subjects without a diagnosis of dementia with regard to benzodiazepine exposure (*i.e.* exposed or unexposed at this date). This analysis concluded that there was an absence of association between benzodiazepine use and dementia (adjusted HR 1.08, 95% confidence interval, 95%CI 0.78 to 1.51) whether the adjustment considered depression or not (Table 17). In this model, the exposed or unexposed status was only assessed at the time of event onset, which was a limited part of the information available on benzodiazepine use. This could have resulted in a non-differential misclassification of exposure since the entire exposure history was not taken into account.

3.3.2.1.2. Second attempt

In a second approach, we considered benzodiazepine exposure both at the time of dementia occurrence as a time-varying determinant and at T_5 (index date for the main analysis). Exposure was classified into four mutually exclusive categories: (i) non-use at the two dates which served as the reference category, (ii) new use at T_5 and use at the event date, (iii) new use at T_5 and non-use at the event date, and (iv) non-use at T_5 and use at the event date. Compared to non-users of benzodiazepines (at the two dates considered), initiators at T_5 with benzodiazepine use recorded at the event date presented an 87% increased risk of dementia. The association was low and statistically non-significant for benzodiazepine users at T_5 with non-use recorded at the time of the event (HR 1.19, 95%CI 0.60 to 2.34). No association was found for subjects exposed at the event date and who had initiated treatment with benzodiazepines after T_5 (HR 0.78, 95%CI 0.50 to 1.21). A complementary adjustment on depressive disorders, made as a sensitivity analysis, did not change the conclusions. These results are detailed in Table 17.

Table 17. Results of a "standard" time-varying Cox proportional hazards model with different definitions of exposure

	Multivariable hazard ratios (95%CI)	
	Model 1*	Model 2*†
Current exposure:		
Non-exposed	1.00 (reference)	1.00 (reference)
Exposed	1.08 (0.78 to 1.51)	1.08 (0.77 to 1.52)
Past initiation at T_5 and current exposure:		
Non-exposed at T_5 and at event date	1.00 (reference)	1.00 (reference)
Non-exposed at T_5 and exposed at event date	0.78 (0.50 to 1.21)	0.78 (0.50 to 1.22)
Exposed at T_5 and not at event date	1.19 (0.60 to 2.34)	1.15 (0.58 to 2.28)
Exposed at T_5 and at event date	1.87 (1.18 to 2.96)	1.93 (1.20 to 3.10)

*Adjusted for age, gender, schooling duration, singleness, wine consumption, use of antihypertensive drugs, use of antidiabetic agents, use of statins, use of platelet inhibitors or oral anticoagulants at baseline (T_5) and Mini-Mental State Examination change between inclusion (T_0) and the three-year follow-up visit (T_3).
†Adjusted for significant depressive symptoms according to Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women) at baseline (T_5).

This second attempt offered the possibility of taking into account the history of benzodiazepine use and not only the use seen at the event date. If initiated in the past and declared at the event date the association was found to be stronger than in the main prospective approach which did not consider exposures after T_5. This approach did not compare the effect of chronic and short-term exposures since, (i) PAQUID did not directly provide durations of exposure; moreover, its cross-sectional character precluded identification of short-term treatments; (ii) on the other hand, benzodiazepine use in the elderly is known to be mainly chronic, making it unlikely that a high rate of short-term exposures had impacted our results (cf. Annexes 4). The stronger association found with the second attempt is probably explained by the higher rate of chronic

users. Indeed, restricting analyses to subjects exposed both at T_5 and at the event date over-represented chronic exposures, while the main prospective approach probably included short-term users less at risk for dementia.

3.3.2.1.3. Finally...

In the framework of a time-varying exposure, a "standard" time-varying Cox proportional hazards model could have been considered. However, the use of such a model could have introduced a bias and was not satisfactory for causal inference under the null hypothesis of no association. Indeed, benzodiazepine use after T_5 (*i.e.* at T_8, T_{13} etc.) would be strongly influenced by prior benzodiazepine exposure status. In that context, using a time-varying Cox model could lead to biased estimates. A typical example is the use of antiviral drugs among patients with HIV when evaluating relevant outcome events.[164] Moreover, estimations could also be biased by the presence of time-dependent confounders which are themselves affected by prior exposure to benzodiazepines.[165] A solution could have been, for example, the use of a weighted model, such as a marginal structural model.[166] However, such a model would require a large group of exposed participants at each time point, which was not possible in the PAQUID cohort.

3.3.2.2. Advanced methodology estimating the influence of time-varying exposure

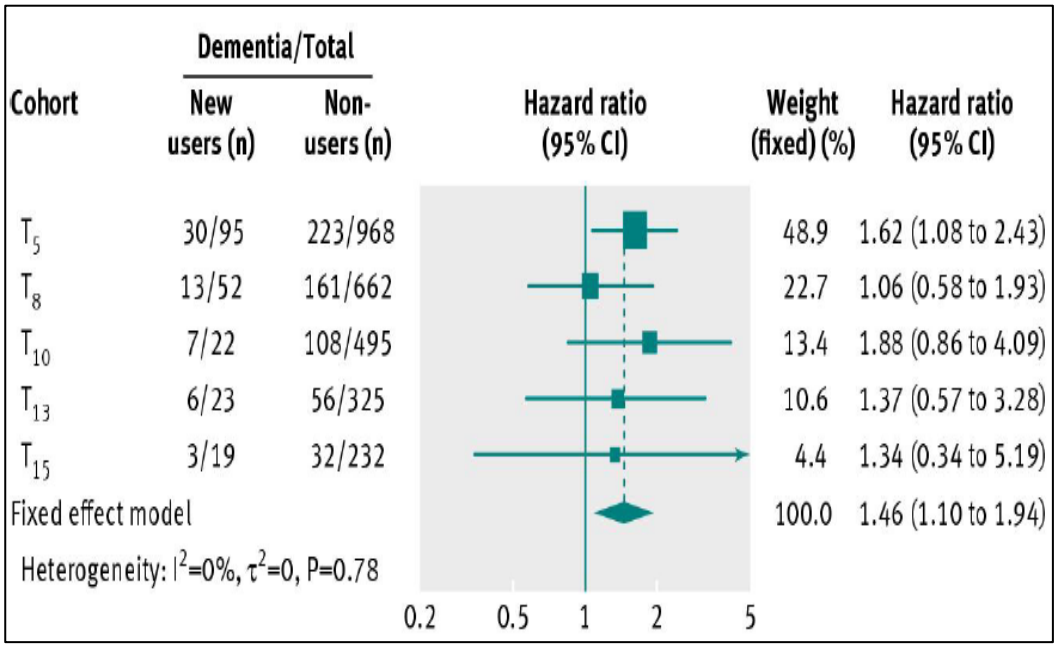
As an alternative to a standard time-varying Cox proportional hazards model, we decided to build several subsequent new initiator cohorts and to follow them until the end of the follow-up. Adjustment on possible confounders was made by using information collected at inclusion in each cohort. This approach enable us to evaluate the changes in the association between benzodiazepine and dementia over time, including changes in covariate structure.

We considered cohorts of new users (participants reporting benzodiazepine use for the first time at the follow-up visit) constituted at T_5, the index date for our main analysis, and at each of the four subsequent dates: T_8, T_{10}, T_{13} and T_{15}. Each subject in each cohort was followed until a censoring event occurred (dementia or death or lost to follow-up) or until the end of the study, whichever came first. For each cohort, we evaluated the association between exposure and the risk of subsequent dementia compared with participants not exposed at index date after adjusting at this date for the same confounders as in the main approach, including depressive disorders. Finally, the five cohorts were pooled using a fixed effect model.

This second approach added a total of 116 new users to the 95 new users at index date (T_5). The pooled multivariable adjusted hazard ratio of dementia was 1.40 (1.06 to 1.85). Additional control for depression did not alter this result (hazard ratio 1.46, 1.10 to 1.94) (Figure VI).

3.3.3. Conclusion of the second prospective approach

Association between new use of benzodiazepines and a subsequent risk of dementia persisted after taking into account the changes in exposure status during follow-up. One should note that the risk did not increase when the delay between exposure start and dementia became shorter, which did not argue for results explained for the most part by a protopathic bias.



*Results adjusted for age, gender, schooling duration, singleness, wine consumption, use of antihypertensive drugs, use of antidiabetic agents, use of statins, use of platelet inhibitors or oral anticoagulants, depressive disorders at the T_5, T_8, T_{10}, T_{13} or T_{15} follow-up visit (index dates), and Mini-Mental State Examination change between the index date and the preceding follow-up visit.

Figure VI. Pooled association between new benzodiazepine use at T_5, T_8, T_{10}, T_{13} and T_{15} and the risk of subsequent dementia* (Billioti de Gage *et al.*[149])

4. Retrospective approach

4.1. Presentation

The results of the cohort studies appeared to be in favour of an association, not obviously biased, between benzodiazepine use and an increased risk of dementia. Considering the impact this conclusion would have if it were causal or partly causal in term of number of attributable cases, we subsequently designed a validation programme within the PAQUID cohort based on a case-control design, which, unlike a cohort design, enabled us to take better account of exposure changes and exposure patterns.

A retrospective approach was retained with the aim of: (1) validating the results of our prospective approach (the credibility of a conclusion is reinforced if confirmed when using a different study design), and (2) refining the definition of exposure to take advantage of the long follow-up available in PAQUID (mainly concerning past exposures, which are probably the most relevant ones under the hypothesis of a causal association).

4.2. Method

4.2.1. Eligibility

Among the 3777 subjects in the PAQUID cohort, those who were still being followed at the eighth- year visit (T_8) following inclusion (T_0), without dementia before this date and with an accurate date of dementia diagnosis, were eligible for the nested case-control analysis.

4.2.2. Case and control definition

Cases were defined by an incident diagnosis of dementia from T_8 onwards. The first date of dementia diagnosis registered in PAQUID was considered as the index date. Each case was matched to up to 4 controls randomly selected among individuals meeting the following criteria: no diagnosis of dementia at the case index date and at the following visit, same gender and same age (± 2 years) as the matched case. Incidence density sampling strategy was applied with the aim of obtaining unbiased estimates.[167 168] In incidence density sampling, each matched control is selected from the study population at risk at the time the event identifying the case (index date for a case) occurs. This method implies that the same control can be matched with several cases and that a case can be a control for another previously diagnosed case.

4.2.3. Exposure

4.2.3.1. Problems of exposure definition

Before retaining the operational exposure definition, we had to deal with several limitations inherent in the PAQUID design. We will describe the main issues and our attempts to circumvent them.

4.2.3.1.1. Missing values

Missing values for exposure linked to unperformed follow-up visits concerned about 25% of individuals included in the PAQUID cohort. Of these, 50% had more than one missing value concerning their exposure status during the follow-up. The concern here was that some of them could be *not missing at random*. For example, subjects with multiple missing values could present a higher risk of dementia.[169] Dealing with this subgroup was tricky: excluding individuals with missing values could convey a possibility of sample distortion bias; not excluding them made it difficult, in some cases at least, to differentiate between users or non-users, which could lead to a misclassification bias. Different solutions were compared:

(1) Exclusion of subjects with missing values

This possibility was acceptable if the rate of missing values was low and equally distributed across cases and controls. If this rate was high, this solution would convey a risk of (i) a loss of information and sample size/statistical power reduction, and (ii) a loss of representativeness and information bias if missing values were not equally distributed across the groups compared.

(2) Imputation of missing values

In an ideal world, this option would avoid the risk of misclassification, loss of information and reduced sample size. In this case, a choice had to be made between full or partial imputation. The first option could lead to a misclassification bias if the rate of missing values was high and/or a high proportion of subjects had numerous missing values. From this point of view, partial imputation under certain conditions seemed more acceptable. Another issue was the imputation process: using automated imputation methods, as proposed by several statistical packages, was appealing although not always under control. In the case of benzodiazepines, the use of which is known to be often chronic, particularly in the elderly

(see part I), a simple deductive method would certainly provide more valid information about the exposure status.

(3) And so?

We decided that individuals with several missing values during their follow-up (making their exposure status unassessable) would be excluded from both groups compared as long as their rate remained ≤5%. In the case of a rate >5%, partial manual imputations would be made. Replacements would be considered only in the case of an exposure measurement missing at one date during the follow-up, the missing variable being replaced by the exposure status observed both at the preceding and following dates if congruent. No imputations would be made for individuals with multiple missing values during follow-up or when the exposure status at the preceding and following dates differed. After imputation, individuals whose exposure status remained unclassifiable would not be excluded but would be analysed in a specific exposure category.

4.2.3.1.2. Heterogeneity of exposure patterns

In the PAQUID cohort, extreme inter-individual heterogeneity was observed with regard to profiles of benzodiazepine use during follow-up. Taking all these exposure patterns into account would have raised the unsolvable issue of the coherence of grouping, and the lack of statistical power. Table 18 illustrates the heterogeneity of exposure patterns during the 20 years of the PAQUID follow-up and the difficulty in constituting homogenous subgroups.

Table 18. Examples of exposure patterns, illustrating the heterogeneity observed during the 20-year follow-up (9 follow-up visits at T_0, T_3, T_5, T_8, T_{10}, T_{13}, T_{15} and T_{20})

Pattern number	T_0	T_3	T_5	T_8	T_{10}	T_{13}	T_{15}	T_{17}	T_{20}	Exposure pattern
1)	1	1	1	1	1	1	1	1	1	**Chronic exposed**
2)	1	.	1	1	1	1	1	1	1	**Chronic exposed**
3)	1	1	.	.	.	X	X	X	X	**Past exposed?**
4)	0	0	0	0	0	0	0	0	0	**Non-exposed**
5)	0	0	.	0	X	X	X	X	X	**Non-exposed?**
6)	0	.	0	.	.	.	0	0	.	**Non-exposed or exposed?**
7)	1	1	.	1	.	.	0	0	.	**Chronic or intermittent exposed?**
8)	1	.	.	0	0	X	X	X	X	**Occasionally exposed?**

1=exposed at time point; 0=not exposed at time point; .=missing at time point; X=lost to follow-up or died at time point.

We made the assumption that imputation of missing values would only be a partial solution to the problem. Therefore, we decided that analyses would be restricted to non-ambiguous exposure patterns *e.g.* 1), 2) or 4) in Table 18, other exposure patterns being either excluded if not too frequent (≤5%) and equally distributed across cases and controls or analysed in a separate category if these two conditions were not met.

4.2.3.2. Exposure definition

The nested case-control design is illustrated in Figure VII.

Two definitions of exposure were considered:

- First, participants were classified as *ever users* when at least one use of benzodiazepines was recorded before the index date.
- Next, ever users were split into: (i) *recent users* defined by a first record of benzodiazepine use at the visit preceding the index date (*i.e.* <5 years before, period B in Figure VII) without any use before, and (ii) *past users* defined by a benzodiazepine use declared at least two visits before the index date or earlier (*i.e.* ≥5 years before, period A in Figure VII).

Remarks:

- In order to preserve a sufficient sample size, and contrary to the cohort design, we did not exclude prevalent benzodiazepine exposures in the nested case-control design.
- We restricted the definition of exposure patterns to the most relevant ones in the context of our study (estimation of the plausibility of a causal association and minimisation of the protopathic bias). Indeed, according to our previous hypotheses, a protopathic bias was more likely to occur for exposures started just a few years before the diagnosis of dementia (*i.e.* <5 years before, period B in Figure VII) than for those started earlier (*i.e.* ≥5 years before, period A in Figure VII).
- Past exposure to benzodiazepines considered both their current use at index date and their discontinuation before this date. We assumed that past exposures were particularly at risk and that studies with larger sample size and providing information on the exposure dose would be needed to interpret the effect of withdrawal.

Never users of benzodiazepines at index date or earlier served as the reference group for the two exposure definitions. We considered all benzodiazepines and related drugs available in France since 1988 (see section 3.2.1.3).

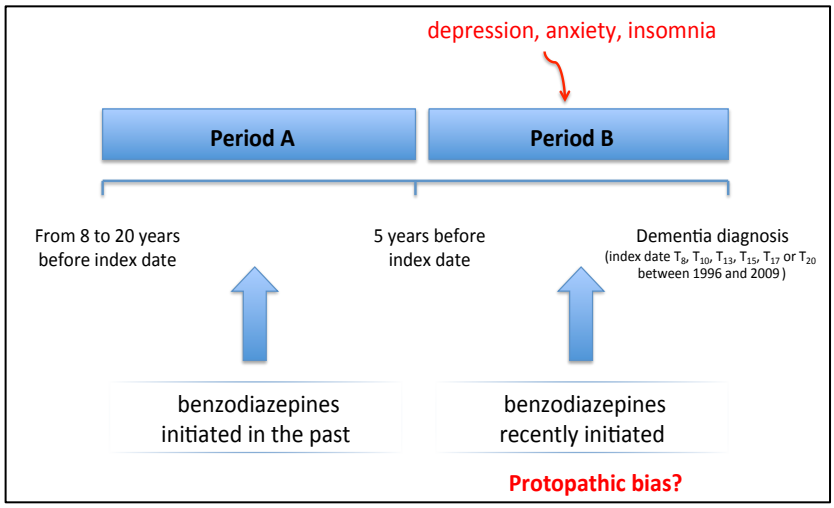


Figure VII. Nested case-control design within the PAQUID cohort

4.2.4. Adjustment

4.2.4.1. Covariates

Independently of matching variables (age, gender) the main risk factors associated with both benzodiazepine use and dementia risk were considered. These factors are: education level (<7 or ≥7 years), marital status, regular wine consumption and cardio-vascular factors (estimated by use of antihypertensive drugs, antidiabetic agents, statins, platelet inhibitors or oral anticoagulants). Further adjustment on depressive symptoms was made in a sensitivity analysis for the reasons explained previously (see 3.2.1.5.3).

4.2.4.2. Time of covariate measurement

The optimal time for measurement of the variables considered as putative confounders was another matter for debate. There were four main possibilities: (1) anytime during the following period, (2) in the period immediately preceding the dementia diagnosis (*i.e.* <5 years before index date, period B in Figure VII), (3) in an earlier period (*i.e.* ≥5 years before index date, period A in Figure VII), (4) considering both recent (period B) and past (period A) periods.

Proposals (1) and (2) were promptly excluded since for our second analysis, past-exposure to benzodiazepines could not have been explained by covariates measured after the start of exposure. Proposal (4) was also excluded because of a possibly high correlation between covariates measured in the two periods which precluded the possibility of introducing the two measures into the adjustment model, as this requires independence between covariates. Consequently, proposal (3) was chosen. Moreover, covariates measured in the past were more likely to predict past exposures than covariates measured closer to the dementia diagnosis. It was also sensible that covariates measured in the past could be satisfactory predictors for more recent exposures to benzodiazepines and could help in controlling for putative early risk factors of dementia. Indeed, dementia has a long latency period, which explains why researchers and clinicians focus more and more frequently on midlife risk factors to identify possible preventive actions.

4.2.5. Statistical analysis

The main characteristics of cases and controls were compared. Association between benzodiazepine use and dementia was estimated using conditional logistic regression adjusted on the main confounders described earlier (see 4.2.4.1). Further adjustments on depressive symptoms were considered in a sensitivity analysis. Two series of models were built, each considering one of the definitions retained for exposure to benzodiazepines.

4.3. Results

4.3.1. Population selection

The selection process is summarised in Figure VIII. Of the 3777 participants in the PAQUID study, 1633 participants followed and without diagnosis of dementia until at least T_8 were eligible for the nested case-control study.

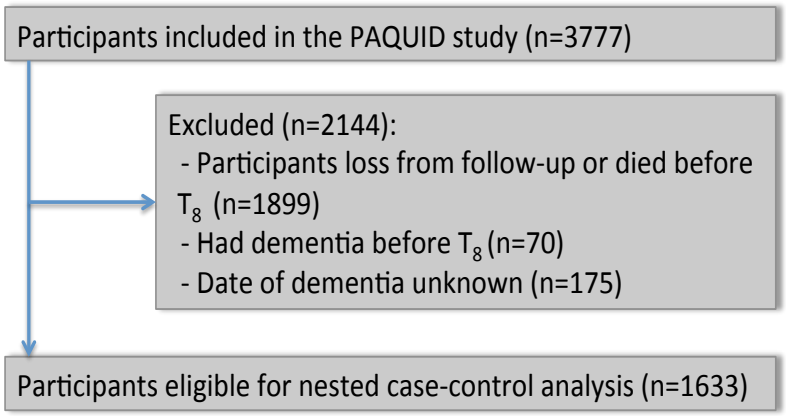


Figure VIII. Identification of participants from the PAQUID study eligible for the nested case-control analysis (Billioti de Gage *et al.*[149])

4.3.2. Comparison of cases and controls

We identified 467 cases and 1810 controls for the nested case-control analysis. Their characteristics are presented in Table 19. Compared to the controls, the cases were more likely to have declared benzodiazepine use (50% *versus* 41%) and mostly in the past (46% *versus* 38%) and to have shorter schooling duration (64% *versus* 74% with duration ≥7 years). No differences were found regarding cardiovascular risk factors, wine consumption, singleness or depressive symptoms.

Table 19. Risk of dementia associated with benzodiazepine use in the nested case-control study of 1633 elderly people from PAQUID study. Values are numbers (percentages) unless stated otherwise (Billioti de Gage *et al.*[149])

Characteristics	Cases (n=467)	Controls (n=1810)
Benzodiazepine ever users	233 (50)	741 (40.9)
Benzodiazepine recent users	17 (4)	52 (2.9)
Benzodiazepine past users	216 (46)	689 (38.1)
Schooling duration ≥7 years	298 (64)	1339 (74.0)
Single or widowed	240/456 (53)	1012/1784 (56.7)
Wine consumption	267/454 (59)	1066/1777 (60.0)
Significant depressive symptoms*	46/450 (10)	153/1778 (8.6)
High blood pressure†	274/456 (60)	1125/1784 (63.1)
Diabetes mellitus‡	29/456 (6)	96/1784 (5.4)
Statin use	26/456 (6)	73/1784 (4.1)
Platelet inhibitor or oral anticoagulant use	32/456 (7)	164/1784 (9.2)

*Based on Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women).
†According to use of antihypertensive drugs.
‡According to use of antidiabetic agents.

4.3.3. Association between benzodiazepine use and dementia

Ever users of benzodiazepines had an increased risk of dementia (adjusted odds ratio 1.55, 1.24 to 1.95). We found a similar association in past users (adjusted odds ratio 1.56, 1.21 to 1.86) and recent users (adjusted odds ratio 1.50, 0.84 to 2.66); differences were significant only for past users. Adjustment on depressive symptoms did not markedly alter the results (Table 20).

Table 20. Risk of dementia associated with benzodiazepine use in the nested case-control study of 1633 elderly people from PAQUID study. Values are numbers (percentages) unless stated otherwise (Billioti de Gage *et al.*[149])

	Cases	Controls	Odds ratio (95%CI)
EVER USE ANALYSIS:			
Univariate analysis:*	**n=467 (%)**	**n=1810 (%)**	
Benzodiazepine non-users	175 (37)	845 (46.7)	1.00 (reference)
Benzodiazepine ever users	233 (50)	741 (40.9)	1.54 (1.24 to 1.93)
Missing exposure	59 (13)	224 (12.4)	1.30 (0.93 to 1.81)
Multivariate analysis:*†	**n=449 (%)**	**n=1771 (%)**	
Benzodiazepine non-users	174 (39)	844 (47.7)	1.00 (reference)
Benzodiazepine ever users	233 (52)	738 (41.7)	1.55 (1.24 to 1.95)
Missing exposure	42 (9)	189 (10.7)	1.04 (0.71 to 1.53)
RECENT / PAST USE ANALYSIS:			
Univariate analysis:*	**n=467 (%)**	**n=1810 (%)**	
Benzodiazepine non-users	175 (37)	845 (46.7)	1.00 (reference)
Benzodiazepine recent users	17 (4)	52 (2.9)	1.58 (0.90 to 2.78)
Benzodiazepine past users	216 (46)	689 (38.0)	1.54 (1.23 to 1.93)
Missing exposure	59 (12.6)	224 (12.4)	1.30 (0.93 to 1.81)
Multivariate analysis:*†	**n=449 (%)**	**n=1771 (%)**	
Benzodiazepine non-users	174 (39)	844 (47.7)	1.00 (reference)
Benzodiazepine recent users	17 (4)	52 (2.9)	1.48 (0.83 to 2.63)
Benzodiazepine past users	216 (48)	686 (38.7)	1.56 (1.23 to 1.98)
Missing exposure	42 (9)	189 (10.7)	1.04 (0.71 to 1.53)

*Matched for age and gender.

†Adjusted for schooling duration, singleness, wine consumption, use of antihypertensive drugs, use of antidiabetic agents, use of statins, use of platelet inhibitors or oral anticoagulants, and significant depressive symptoms according to Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women), 7 or 8 years before index date.

4.4. Conclusion

The results of the nested case-control study were congruent with those of the prospective approach (both for the direction and the strength of the association). Moreover, the association was statistically significant for benzodiazepine users who initiated their treatment in the past but not for initiators in the few years preceding the dementia diagnosis. These results rather argue against an association explained for the most part by a protopathic bias.

5. Discussion

5.1. Main conclusions

From our main prospective study, based on a random population sample of elderly people, we concluded that the risk of dementia increased by 60% in benzodiazepine initiators. This result did not seem to be explained by a protopathic bias or reversed causality for the following reasons:

- The excess risk appeared 5 to 8 years after treatment initiation (in the main prospective approach).
- An adjustment was made on the cognitive level measured by three different tests (MMSE, Benton, Isaac) 3 to 5 years before the inclusion in both exposed and non-exposed groups. This avoided the risk of over-representing subjects with an advanced prodromal phase in the exposed group.
- The association remained consistent when we pooled five cohorts of new benzodiazepine users throughout the 15 years of follow-up in the second prospective approach. Moreover, in this analysis we did not observe an increase in risk when the delay between treatment initiation and dementia diagnosis became shorter.

The results of the nested case-control study, used as a validation study, were in accordance with those of the prospective approach: the association between benzodiazepine use and dementia was found to be around 56% and related to past-initiation of benzodiazepines. No statistically significant association was found for recent users, which is not in favour of results mostly explained by a protopathic bias.

5.2. Strengths of the studies

These PAQUID studies had several strengths. First, they were based on a long follow-up allowing identification of delayed effects of exposure to benzodiazepines. Second, the diagnosis of incident dementia cases was particularly robust (based on validated DSM-III-R criteria[143] and ascertained by senior neurologists blind to the study hypothesis). The ascertainment of benzodiazepine exposure was also robust: recorded by trained interviewers and validated by inspection of the medicine packages at the patient's home. Third, the main prospective approach preserved an observation period before inclusion which allowed for adjustment on factors

strongly associated with benzodiazepine use and also considered as predictors of a future dementia. Finally, these studies were carried out in a large representative cohort of elderly participants[147] with adjustment on numerous potential confounders of the benzodiazepine-dementia association.[130 148 150 151]

5.3. Limitations of the studies

Excluding prevalent users of benzodiazepines resulted in a rather limited sample size of exposed (n=95) and therefore made the statistical power too low for subgroup analyses and ruled out the possibility of assessing the effect of different benzodiazepines or of their elimination half-life (use of long-acting benzodiazepines is not recommended in the elderly because of a risk of accumulation in the brain, leading to toxic levels).

Information about anxiety and sleep disorders, both potential prodromes of dementia and highly correlated with benzodiazepine use, was not specifically recorded in the PAQUID programme. As a consequence, adjusting separately for these symptoms was not possible. Interestingly, the CES-D scale[156] includes questions about anxiety and insomnia which could have been used for adjusting for these conditions. However, entering three separate scores (*i.e.* for depression, anxiety and insomnia) in the models would have raised a concern about colinearity, as depressive symptoms are often associated with anxiety and/or sleep disorders, mainly in elderly people.

In the prospective approach, we logically excluded individuals with missing exposure status at index date (T_5) or before (T_3 or/and T_0). As these missing data were possibly linked to unperformed follow-up visits explained by a pre-demented or demented state, a putative selection bias could have occurred.[169] However, since the excluded subjects had a lower schooling level and were more likely to live alone (two factors known to be associated with the risk both of benzodiazepine use and of dementia, cf. Part I) such a selection bias would have tended to decrease the strength of the association and therefore to be conservative.
Finally, reverse causation cannot be entirely ruled out as an alternative explanation for our results, even if we believe for the reasons mentioned earlier that there was no convincing argument for such a spurious association. A dose-effect relationship, a strong argument for drug causation, could not be researched since no information about dose exposure was available in the PAQUID programme; moreover, precise estimation of exposure duration would imply hypotheses which could lead to misinterpretations.

6. Complementary questions

6.1. Reviewers' questions

Before accepting the manuscript for publication, numerous questions were addressed by the reviewers of the British Medical Journal. As these questions were for the most part quite methodologically relevant, we summarise below the answers to their main comments.

6.1.1. About reverse causality bias

Comment 1: Isn't benzodiazepine use nothing more than an early marker of beginning dementia?

In the present case, assessment of a putative protopathic bias and reverse causation was made particularly tricky by the absence of clear-cut information about the length of the prodromal phase of dementia and the actual role of pre-existing depression, anxiety or sleep disorders, both presented in the literature either as a prodromes or as risk factors.

Therefore, there is obviously a possibility that the association found in our study was explained, at least in part, by reverse causality. However, we do not think that this possibility is driving the results of our study because: (i) the long duration of follow-up made it possible to study, both in the cohort and case-control approaches, the effect of exposures started a long time (>10 years) before the diagnosis of dementia; (ii) for the main analysis, only new initiators were considered and a 3- to 5-year "run-in" period was kept in order to improve adjustment at inclusion, *i.e.* before exposure, including variables such as cognitive decline during the 5 preceding years.

However, even if benzodiazepines were nothing more than an early marker of a future dementia, our findings would still be of interest for public health and disease management, since they indicate that a new benzodiazepine user would have 50% more chance of developing dementia within the next 15 years than a non-user at this date. Patients on benzodiazepines may therefore have to be followed more closely for the development of dementia.

Comment 2: By beginning the analysis at T_5 the case against protopathic bias is undermined.

This point was extensively discussed by the authors when designing the protocol of the present study. It was tempting to start with subjects found exposed at T_0 with 2 clear advantages: a much larger sample size for the exposed group and a longer follow-up (20 years instead of 15). This option was discarded (mainly) for the following reasons: (i) considering prevalent users precluded any knowledge about the date of exposure and consequently the use of survival curve

analysis (one of the main objectives of our study), (ii) adjustment before or at the date of first exposure was impossible, (iii) subjects found exposed at T_0 could have been "survivors" from a past-exposed population, *i.e.* those not having presented dementia until T_0 (depletion of susceptible bias). The selected option allowed, at the expense of a markedly reduced sample size and a shorter follow-up (15 years instead of 20), a much more satisfactory control for putative confounders and protopathic bias by (i) restricting analyses to new users (at least to those not exposed at T_3), which allowed a precise description of survival times for exposed and non-exposed groups, (ii) allowing a satisfactory control at inclusion, including changes in MMSE scores between T_0 and T_3.

Comment 3: I don't believe they were able (or would be able) to fully deal with the issue of reverse causality/ protopathic bias. Alzheimer pathology is likely present for a decade or more before even the first cognitive symptoms arise. They in turn can go on for years before they progress to the point where a dementia can be diagnosed. I'm not sure using the three brief cognitive measures (MMSE, Benton, Isaacs) would have been sufficiently sensitive to change to protect against missing evolving cognitive loss. As well affective and behavioural issues as they note can arise before cognitive ones in incipient dementia. I don't think this can be entirely eliminated as a potential explanation of any found association between benzodiazepine use and dementia. In observational studies, correlation does not prove causation. I don't think a long delay would necessarily "plead" against other explanations.

Ruling out reverse causality or protopathic bias is made particularly difficult in the case of dementia. Moreover, there is no clear-cut information about the length of the prodromal phase of dementia and the actual or putative role of pre-existing anxiety, both of which are presented in the literature either as a prodromal or as a risk factor. However, on the other hand, a randomised controlled trial, maybe the only conclusive design in terms of causality, would not be feasible for obvious ethical and practical reasons. Even if conveying the inescapable limitations of an observational approach, we think that our study design avoids most of the limitations of previously published studies. First, we were lucky enough to have access to all the data from the PAQUID programme, a large prospective cohort studying cognitive aging at the population level. It has the following particular strengths: (i) follow-up of 20 years, (ii) outcome based on a robust diagnosis, (iii) drug exposure ascertained by both face-to face interviews and inspection of drug packages, (iv) extensive collection of data at each of the 9 dates of follow-up for more than 3700 subjects representative of the general population. We agree with the fact that some missing variables, tests or scales would have allowed a more robust assessment of the plausibility of a reverse causality. However, we think that the amount of relevant information available from the PAQUID programme is already remarkable for an observational study.

Moreover, it would have been impossible to extend the amount of information for the purpose of our study: a follow-up as long as 15 years imposed a design based upon already recorded data.
While not ruling out the possibility of a non-causal association, we think that our results clearly do not support such a hypothesis. Despite an adjustment made at the beginning of exposure, including CES-D, Isaac, Benton and MMSE changes between T_0 and T_3, an excess risk was observed for exposed patients followed for 10 years and more, a time lag that does not argue for a protopathic bias. This is also illustrated by the survival curves.

6.1.2. About other confounding

Comment 4: Some explanation of why they chose these specific covariates (other than age and gender) and the categorization scheme (changing continuous to categorical data is often not a good idea) used for some of them (other than the CES-D) would have been helpful. It is a shame that they didn't report on sleep symptoms or anxiety, the primary indications for benzodiazepines. A variety of other important confounders were not reported (e.g. family history, closed head injuries - which some might argue could explain the association as the use of benzodiazepines is associated with a higher fall risk).

4a. The selection of covariates considered for adjustment ensued from two main criteria: (i) known to be or suspected of being associated with both the probability of using benzodiazepines and the risk of dementia, (ii) to be available from the recorded data in the PAQUID database. Except for anxiety and insomnia (see specific responses below) we do not think we missed any relevant potential confounders (see the specific response for family history, falls and smoking habits below).

4b. For the use of categorical/continuous variables, some were typically continuous and used as such, *e.g.* MMSE. Others were typically discrete (gender, living alone, using cardiovascular drugs or antidiabetics) and were used as such. For the following variables we chose to use previously proposed meaningful cut-offs: CES-D, schooling duration, alcohol consumption.
For CES-D, in order to avoid aberrant distribution problems, we used the threshold proposed and validated as a reference in the literature: 17 and over for men, 23 and over for women.[156]
As suggested, Benton and Isaac's tests, used in addition to the MMSE in order to minimise possible differences across groups, are now used on continuous variables without significant alteration of the results.
For schooling duration, using a single threshold of 7 years could appear simplistic. In fact, one should bear in mind that the studied population was composed of people included in the PAQUID programme between 1987 and 1989 when aged 65 and over. Therefore, the dates of

birth for the youngest ranged from 1922 to 1924; in the first decades of the 20th Century and in the farming communities in South Western France, very few people went to College or University. Therefore, the 7-year cut-off was the most relevant choice.
For alcohol, we were more interested in regular wine consumption (typical in a French population of this age) and assessed as YES/NO rather than in intermittent or acute consumption.

4c. We agree about the lack of specific adjustment on sleep disorders and anxiety. The reason is clearly that these disorders were not specifically explored by the various questionnaires or scales used in the PAQUID programme. However, these symptoms are considered in the CES-D questionnaire. We did not extract these specific responses from the CES-D questionnaires since this test was conceived as a global score exploring both depressive symptomatology and anxiety/insomnia. Moreover, after having extensively discussed this point with senior neurologists and psychiatrists, entering three specific scores in the logistic model (one for depression, one for anxiety and one for sleep disorders) could have been open to criticism because of an expected colinearity, depressive symptomatology being associated more often than not with sleep disorders and anxiety, mainly in the elderly.

4d. We did not enter family history of dementia in the model since there was no argument in favour of its association both with the risk of dementia and the probability of being treated with benzodiazepines. The answer is likely to be “YES” for the first and “NO” for the second. Therefore, we would not consider it as a potential confounder. Nevertheless, we checked whether there were significant differences for this parameter between exposed and non-exposed groups and the answer is “NO”. For example, history of memory impairment or loss was found in 20% of exposed *versus* 23% of controls (P=0.57). History of speech disorders was found in 10% of exposed *versus* 11% of controls (P=0.74). For orientation disorders, we found 7% in exposed and 5% in controls (P=0.66).

4e. For closed head injuries, we confess we did not record this information. Such a trauma is known to increase the risk of subsequent dementia. From a causality point of view, it would not be an argument against the putative causal role of benzodiazepines since in this case, closed head injury would likely be in the causal pathway between benzodiazepine use and dementia (thus, by definition not a confounding factor). However, without minimising this factor, it is likely that the number of closed head injuries, if any, was quite small in the exposed group. Indeed, a study we conducted in the PAQUID programme on the association between falls and benzodiazepine use (Pariente A. Drugs and Aging. 2008)[76] found 382 cases of injurious falls during a follow-up of 10 years of the 3777 PAQUID participants; 69, *i.e.* 1.83% corresponded to head injuries (not only closed head injuries). That means we can expect 1 or 2 cases among the

95 subjects in the "new initiators" group.

Comment 5: Is smoking a relevant confounder?

Although this information was available from the PAQUID study, we did not consider smoking status (cigarette, pipe or cigar) in our initial models as we believe smoking is not a strong biological confounder on the association under study (cf. Part I). Indeed, further adjustment on this variable did not significantly alter the results, the HR value moving from 1.60 (1.08 to 2.38) to 1.56 (1.03 to 2.36).

6.1.3. About exposure to benzodiazepines

Comment 6: If the analysis were repeated, beginning at T_3, the argument against protopathic bias would be stronger.

As mentioned above, we chose T_5 as the index date after considering all other possible options. Again, we were aware of the constraints and limitations of this choice but were convinced that it had the best pros/cons ratio. Clearly, the T_3 cohort scheme would have had two main advantages: a larger number of "new initiators" and a longer follow-up (17 years instead of 15). On the other hand, this design would have been plagued by several drawbacks, some of them being crippling from our point of view. As previously mentioned, the main reason for discarding T_3 as inclusion date was that it did not fit the main requirement for our study: to secure a period of at least 3 years before inclusion in order to allow measurement of variables, *e.g.* MMSE and CES-D scores, on at least 2 dates before inclusion and beginning of exposure.

Comment 7: I wonder how their initiators of benzodiazepines (n=95) compared to the prevalent users (n=735). The latter group made up the majority of benzodiazepine users in their study. This was another potential comparison group.

It was obviously tempting to start with subjects found exposed at T_0 (prevalent users) with two clear advantages: a much larger sample size for the exposed group (735) and a longer follow-up (20 years instead of 15). This option was ruled out (mainly) for the following reasons: (i) considering prevalent users precluded any knowledge about the date for exposure start and consequently the use of survival curve analysis (one of the main purposes of our study), (ii) adjustment before or at the date of first exposure start became impossible and adjustment at T_0 (after several years of benzodiazepine use for most subjects) was meaningless, (iii) subjects found exposed at T_0 could have been "survivors" from a past-exposed population, *i.e.* those not having presented a dementia until T_0 (depletion of susceptible). The selected option (inclusion

at T_5) provided, at the expense of a markedly reduced sample size and a slightly shorter follow-up (15 years instead of 20), a much more satisfactory control for putative confounders and protopathic bias by (i) restricting analyses to new users (at least not exposed at T_3), which allowed a precise description of survival times for both groups, (ii) allowing a satisfactory control at inclusion, including changes in MMSE scores between T_0 and T_5.
Similarly, inclusion at T_3 would have also provided both a slightly longer follow-up and a larger exposed population. This option was also ruled out, the main reason being that it did not fit the main requirement for our study: to secure a period of at least 3 years before inclusion in order to allow measurement of variables, *e.g.* MMSE and CES-D scores, on at least 2 previous dates.
We have added a nested case-control study not excluding prevalent use. The results are very similar to the cohort approach.

Comment 8: The authors did not distinguish between short-term, intermittent, or continuous use of benzodiazepines in their main analysis. Dose (adjusted for individual agents) wasn't considered either. I would have thought cumulative exposure would have been an important variable to consider. While it would have been nice, I understand the practical limitations they would face in looking at individual benzodiazepines or even categories of these agents (e.g. short versus long-acting).

We have added a case-control analysis to evaluate the association between current and more recent users. However, dosing and long-term exposure cannot really be addressed in the PAQUID programme.

Dosage: unfortunately, PAQUID did not record information on drug dosing, so we cannot provide results for this question.

Cumulative exposure: we are not sure that being exposed at, for example, two time points three years apart would mean that a person has a cumulative exposure of 3 years. Thus, we decided not to include such an analysis in our paper as interpretation would be difficult.

Individual benzodiazepines: lastly, for obvious reasons (mainly statistical power), it was not possible to compare the risk of dementia associated with different molecules or categories of benzodiazepines. However the whole benzodiazepine family shares the same pharmacological properties and acts on the same GABA receptors sub-types.[77]

6.1.4. About various points

Comment 9: It wasn't clear to me what was the degree of attrition among study participants. There must have been some and I wonder if it was equivalent (and for the same reasons) in the benzodiazepine users and non-users.

There is obviously attrition during this long-term follow-up (15 years) of a fixed population aged 70 and more at inclusion (T_5). The durations of follow-up were similar for exposed and non-exposed groups. The mean (years, SD) was 6.57 (5.12) for "new initiators" and 7.20 (5.48) for non-exposed. Median (IQR) was 6.15 (2.18 to 10.45) for "new initiators" and 6.18 (2.63 to 12.53) for non-exposed. These figures become quite close when considering the excess risk of dementia in the exposed group, which led to a slightly shorter survival time.

Comment 10: What is the clear message for doctors? Is it helpful or harmful to use these drugs?

This point is particularly relevant. On the one hand, when considering the high incidence of dementia and the high prevalence of benzodiazepine use, it is sensible to make doctors aware of the possibility of an increase in the risk of dementia associated with these treatments. On the other hand, it is clear and proven that these drugs can be valuable, if not essential, for many patients. Moreover, to present benzodiazepines as an evil could lead to a massive switch towards drugs associated with other but certainly higher risks, such as antipsychotics. The main target of the message from our paper is (i) to carefully assess the individual benefit/risk ratio before prescribing, (ii) to systematically reconsider the justification of maintaining long-term treatments (6 months and over), mainly in the elderly.

Comment 11: Assessments every 2-3 years and index date taken to be mid-point between no evidence and evidence of dementia. Why wasn't an interval censored Cox model used? Would this give different results?

It is impossible to assign an exact date of start of dementia, which is also true for the clinical setting. However, as we have no reason to believe that the date of onset of dementia is different for benzodiazepine users and non-users with respect to our follow-up time points (*i.e.* they follow a random pattern), the results of an interval censored model would not differ. In addition, the association between benzodiazepine use and risk of dementia was confirmed in our nested case-control study approach with very similar effect estimates.

Comment 12: Curiously the effect of combining the cohorts is smaller than for the main analysis. This suggests either that the secondary analysis is less sensitive or that duration or timing of benzodiazepine use is important.

The comment is correct: one may observe a (small to modest) decrease in the strength of association for cohorts with the shortest length of follow-up. We also agree with the hypotheses suggested, even if it would be unwise to provide a clear-cut opinion here. Some remarks: (i) if confirmed, the strength of association being stronger for the cohorts with the longest follow-up would argue against a protopathic bias, (ii) nevertheless, one should be cautious here since, on account of their respective sample sizes, none of the T_8 to T_{15} cohorts provided the statistical power for robust effect estimates.

6.2. Comments following the publication of our research

Our article was published by the British Medical Journal in an *open access* mode. A significant part of the comments made by the readers were the same as those previously made by the reviewers and discussed above. In the three paragraphs below, we discuss some relevant points and additional analyses that we conducted.

6.2.1. Influence of elimination of the molecules

After the publication of our study, and in order to answer several recurring questions, we estimated the risk of dementia in new users after having taken into account the elimination half-life of the molecule used. The new users group (n=95) was split into two categories: (i) initiators of benzodiazepines with long elimination half-lives (≥12h) at T_5, and (ii) initiators of benzodiazepines with short half-lives (<12h) at T_5. Users combining products with short and long half-lives were logically classified in the long half-life group. Both groups were compared to non-initiators with regard to incident risk of dementia and by using the methodology previously described for the main prospective approach.

Survival curves for each category of users (*i.e.* taking into account the elimination half-life of the molecule used) and non-users of benzodiazepines are represented in Figure IX.

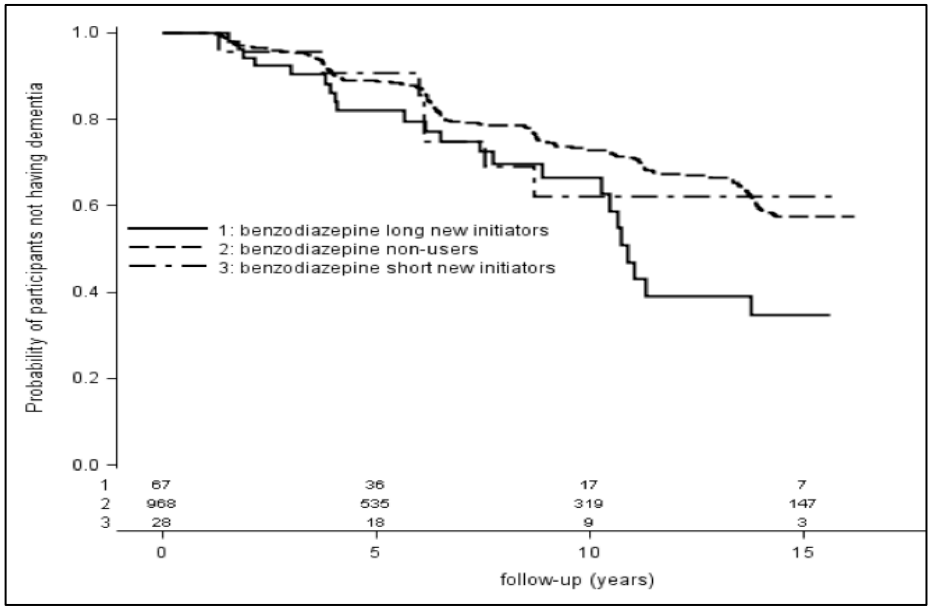


Figure IX. Dementia-free survival in the PAQUID study in new users of benzodiazepines and non-users at baseline (fifth year). Influence of elimination half-life

Among the 95 new initiators of benzodiazepines at T_5, 28 subjects (29.5%) used short-acting benzodiazepines and 67 (70.5%) used long-acting ones. We found a significantly increased risk of dementia in the group using long-acting benzodiazepines (adjusted hazard ratio, HR 1.78, 95% confidence interval, 95%CI 1.14 to 2.80). The risk was lower and not significant for the group of initiators of short-acting benzodiazepines (HR 1.20, 95%CI 0.52 to 2.75).

6.2.2. Influence of mortality rates on the estimates

In order to answer several comments, we performed a series of additional analyses to assess the putative influence of an unbalanced mortality rate between groups on the estimates. Owing to the relevance of this matter, the methodology used and the results are presented in a special topic (cf. Part V, section 2).

6.2.3. Influence of other psychotropic use on the estimates

To answer several comments we also performed various complementary analyses in order to estimate the possible influence of the use of other psychotropics on the risk of subsequent dementia. The methodology used and the results are presented in a special topic (cf. Part V, section 3).

7. Summary, conclusion and additional questions

The BENZODEM programme was conducted within the French PAQUID cohort among individuals aged 65 and older, and consisted of two cohorts and one case-control study. We found a consistent and statistically significant risk of dementia which was increased by about 50% in benzodiazepine users. This increase in risk seemed for the most part not to be explained by protopathic bias, which was the main criticism levelled at earlier studies.

The BENZODEM studies added new arguments in favour of an unbiased association between benzodiazepine use and dementia. However, further questions remained unanswered although they would be useful in assessing the possibility of a direct link and to provide valuable indications to clinicians and patients about potentially at-risk patterns of use:

- Is there a dose-effect relationship (which is a strong argument for drug causation)?
- Would adjustment on other prodromes of the disease make the estimation different?
- Does the type of molecule used influence the results?
- What is the most likely mechanism for explaining the relation observed?

The three studies conducted in the context of the BENZODEM programme led to a publication in the British Medical Journal in September 2012.[149]

PART IV – The BENZODEM2 study (RAMQ database)

1. Context and objective

1.1. The context in a few questions

WHAT DO WE KNOW?

Five observational studies have highlighted an increased risk of dementia in benzodiazepine users. For most studies, imperfect controlling for reverse causality bias could have explained the positive results observed by the authors. Indeed, treatments initiated a few years before the diagnosis of dementia could possibly not be the cause of the disease but could have been motivated by some of its prodromes, since they are also indications for prescribing benzodiazepines (anxiety, depression, insomnia) (cf. Part II).

The BENZODEM programme confirmed these findings and provided supplementary arguments against results being essentially explained by a reverse causality or a protopathic bias (cf. Part III).

WHAT DO WE NOT KNOW?

The fact that information about the doses of the medicines used was not available in the PAQUID cohort precluded any possibility of researching a dose-effect relationship, despite this being a compelling argument for the causal assessment of a potentially drug-induced outcome (cf. Part III).

WHAT ELSE?

Conclusions from BENZODEM raised new issues about possible differences in risk of dementia for the various patterns of benzodiazepine use.

The French Ministry of Health (Direction Générale de la Santé, DGS) encouraged us to go further, with more researches and granted a part of a new research programme.

To provide a good opportunity to explore unanswered questions, a new database was needed, providing data that could identify patterns of use that were at risk, *e.g.* type of molecule, effect of dose and duration of treatment. These data should be easily and quickly accessible, as setting up an *ad hoc* programme was not conceivable.

1.2. Objective

In order to increase our knowledge about the relationship between benzodiazepine use and dementia, we designed a second programme called BENDODEM2 using the claims database of the "Régie de l'Assurance Maladie du Québec (RAMQ)". This programme aimed at (1) testing the reproducibility of results obtained from the BENZODEM programme by using a different population, and (2) assessing the strength of the association according to dose, duration of treatment and elimination half-life of the molecule used and minimising the impact risk of a protopathic bias on the results.

1.3. Hypotheses

Several hypotheses were considered and assessed:

- Benzodiazepine exposure increases the risk of dementia (the main question being: how would the results of the BENZODEM2 study compare with those of the BENZODEM programme?).

- Dementia risk increases with the dose and/or duration of exposure to benzodiazepines. If verified, such a finding would be a valuable argument for drug causation.

- Molecules with long elimination half-lives have more deleterious effects on cognition than short-acting ones. Such a finding would be another argument for drug causation. Indeed, benzodiazepines with a long half-life tend to accumulate in the organism, which results in a more constant impregnation of brain tissues than for molecules with a short half-life.

As for BENZODEM, we assumed that exposures started long before the outcome (particularly those initiated more than 5 years before the dementia diagnosis) are less prone to contribute to a protopathic bias. Indeed, the probability of a symptom that has motivated a benzodiazepine prescription *i.e.* anxiety, depression or insomnia, being a prodrome of the disease is likely to decrease with the time lag between these two events.

2. Study population: the RAMQ cohort

2.1. Presentation

The study was conducted using the medical and pharmaceutical services claims database of the Quebec Health Insurance Agency (RAMQ). The RAMQ health insurance plan is universal as it covers all permanent residents in the province of Quebec, regardless of age and income for both physician services and hospitalisation. The resulting RAMQ medical service database includes the date, the origin (private practice, emergency department, hospital, long-term care unit or institution) of all medical services and procedures (coded according to the Canadian classification of diagnoses, therapeutic, and surgical procedures) billed on a fee-for-service basis. This health care programme is complemented by a public drug plan covering 97% of the residents aged >65 years. The RAMQ pharmaceutical service database contains information from pharmacy claims for dispensed medications reimbursed by the programme, but not for medications prescribed in a hospital. This database includes information on the name of the drug, number of dispensed units, dosage, prescribed duration, and speciality of the prescriber.

2.2. Advantages of the RAMQ cohort

The RAMQ cohort was of great interest for our study project since it provides the following advantages:

- A large number of recorded events. Thus several subgroup analyses were possible considering various parameters for the definition of exposure (*e.g.* dose, duration of use, half-life of the molecule).
- Data are highly representative of the elderly population of Quebec (>65 years).
- Unlike the PAQUID study, dosage and duration of drug use are recorded.
- Data are collected continuously, unlike the PAQUID programme where follow-up consists of cross-sectional assessments every 2 or 3 years.
- The RAMQ prescription claims database is known to be accurate and comprehensive concerning drugs dispensed to participants.[170]
- The base contained a lot of information concerning drug prescription and medical diagnoses, which are essential in order to control for confounding factors and adjustment models.

2.3. Limitations of the RAMQ cohort

Bearing in mind the main objectives of our research programme, some limitations inherent in the RAMQ databases should be mentioned:

- Events are defined using the International Classification of Diseases 9th version (ICD-9) codes reported by clinician. However, diagnoses based on recorded data may be less robust than those confirmed by an independent qualified physician, as was the case for dementia in the PAQUID programme. Moreover, there could be a delay between the actual onset of the disease and its being recording in the database.
- Tailored and additional extractions from the RAMQ database are expensive and may require a long delay. For time and cost considerations, we used data previously extracted for another purpose, which made adaptation to the design chosen for the study more complex.

3. Methodological approach

3.1. Design and source population

3.1.1. Choice of the design

A nested case-control study was undertaken among community-dwelling elderly residents (age >66) living in the province of Quebec (Canada) and who were members of the public drug plan between January 1st 2000 and December 31st 2009. A nested case-control design, *i.e.* using pre-recorded data over a long period, combines the advantages of a retrospective design (mainly the possibility of exploring several definitions of exposure) and a level of proof that is as good as for prospective studies (the design consists of a retrospective analysis of data collected prospectively, *a priori* without the possibility of recall bias).

3.1.2. Source population

The source cohort combined two cohorts corresponding to two distinct random extractions from the RAMQ database:

- One cohort of 37,611 elderly persons (>66 years) with reimbursement claims for a treatment relative to dementia (*i.e.* cholinesterase inhibitors or memantine) between 2000 and 2009 (Exposed cohort, EC).
- One cohort of 87,389 elderly persons (>66 years) without reimbursement claims for such a treatment between 2000 and 2009 and split into two subgroups: (i) those without any medical diagnosis of dementia during the period (n=86,259), (ii) those with a medical diagnosis of dementia during the period (n=1130). (Non-exposed cohort, NEC).

Chronology and details relative to the different extractions of the EC and NEC samples are described in Table 21.

Table 21. Details of extraction of patients exposed to anticholinesterases (Exposed cohort, EC) and patients not exposed to anticholinesterases (Non-exposed cohort, NEC)

Phase	Cohort selected	Period of selection	Period of extraction	Number (n=)
A	Cohort of individuals treated with cholinesterase inhibitors (EC*)	2000-01-01 2007-12-31	1999-01-01 2007-12-31	27,722
B	Follow-up of individual included in EC* during the phase A	Not applicable	2007-01-01 2009-12-31	27,722
	New individuals included in EC*	2008-01-01 2009-12-31	2007-01-01 2009-12-31	9,889
	Cohort of individuals not treated with cholinesterase inhibitors (NEC†)	2000-01-01 2009-12-31	1999-01-01 2009-12-31	87,389

*Exposed Cohort
†Non-Exposed Cohort

We assumed that by pooling two cohorts which were representative of the populations that were exposed and not exposed to cholinesterase inhibitors, this would provide a representative source of cases (treated and not treated) and a representative source of controls, *i.e.* without dementia and not treated with an antidementia drug at the date of dementia diagnosis of the corresponding case (index date).

3.2. Case definition and measurement

3.2.1. Cases of Alzheimer's disease

The case definition focused on incident cases of Alzheimer's disease during the study period. Each case was identified through a first diagnosis of Alzheimer's disease using the International

Classification of Diseases (ICD-9: 331.0). Other types of dementia (Table 22) were excluded even if associated with a diagnosis of Alzheimer's disease.

The reasons for excluding other and mixed types of dementia were the following: (i) Alzheimer's disease is, by far, the most common type of dementia, (ii) mixing dementias of various origins, *i.e.* Alzheimer, vascular, Lewy bodies, etc., characterized by different pathophysiological mechanisms, would have resulted in a less precise case definition and a less relevant assessment of the association with benzodiazepines, and (iii) in contrast to previously published studies, the large study sample available from the RAMQ made this distinction possible.

Table 22. Non Alzheimer's dementia and corresponding ICD-9 codes

Non Alzheimer's dementia diagnoses	ICD-9 Code
Senile dementia uncomplicated	290.0
Presenile dementia	290.1
Senile dementia with delusional or depressive feature	290.2
Senile dementia with delirium	290.3
Vascular dementia	290.4
Frontotemporal dementia	331.1
Dementia with Lewy bodies	331.82

3.2.2. Minimisation of cases with late report of Alzheimer's diagnosis

As for all studies conducted using claims databases without direct access to patients, there could have been a delay between the actual date of onset of the Alzheimer's disease and the date of its recording (index date for our study). For that reason, cases with reimbursement claims for an antidementia drug recorded before the first diagnosis of Alzheimer's disease were excluded. This was decided in order to minimise the inclusion of cases for which recording of the diagnosis was delayed, as this time lag could be suspected of increasing the probability of protopathic bias.

3.2.3. Cases with long follow-up

Subjects entered in the RAMQ database less than 6 years before the first diagnosis of Alzheimer's disease were also excluded. Consequently, all subjects had a minimal duration of follow-up of 6 years, 10 years being the maximum. This choice was made under the assumption that the prodromes of the disease potentially associated with benzodiazepine prescription (*i.e.* anxiety, depression, insomnia) are more likely to appear in the 5 years preceding the diagnosis of dementia.[29 139 140]

3.3. Definition of controls

Controls were randomly selected among individuals from the same population as the cases. Each case was matched at the index date with four controls using an incidence density sampling strategy with the aim of obtaining unbiased estimates.[167] [168] Controls fulfilled the following criteria: (i) no Alzheimer's disease or anticholinesterase reimbursement till index date and one year after, (ii) same gender as the matched case, (iii) same age group (70 to 74, 75 to 79, 80 to 84 or ≥85) as the matched case, and (vi) same duration of follow-up (6, 7, 8, 9 or 10 years) as the matched case.

3.4. Exposure definition and measurement

3.4.1. Measurement in the RAMQ database

Benzodiazepine use was assessed using dispensation claims recorded in the RAMQ database. All benzodiazepines included in the RAMQ list of reimbursed medications during the study period were considered (Table 23).

Table 23. Elimination half-lives and main indication for benzodiazepines reimbursed by the RAMQ between 2000 and 2009 (Billioti de Gage *et al.*[149])

Indication	Long-acting (half-life ≥20h)	Short-acting (half-life <20h)
Anxiolytic	Bromazepam (20h) Chlordiazepoxide (5-30h) Clobazam (20h) Diazepam (32-47h)	Alprazolam (10-20h) Lorazepam (10-20h) Oxazepam (8h)
Hypnotic	Flurazepam (120-160h) Nitrazepam (16-48h)	Midazolam (1.5-2.5h) Temazepam (5-8h) Triazolam (2h)
Anticonvulsant	Clonazepam (20-60h)	

3.4.2. Observation period

3.4.2.1. Decision

As justified above, a minimal duration of follow-up of 6 years was a prerequisite for inclusion. That enables us to restrict the comparison of cases and controls to exposures initiated more than 5 years before the index date. Two remarks should be made:

- The effect of benzodiazepines initiated in the 5 years preceding the clinical diagnosis have already been assessed by the case-control study of the BENZODEM/PAQUID programme. Consequently, there was no need to reply to this evaluation in BENZODEM2. Indeed, the main purpose of BENZODEM2 was not to compare recent and past initiation of benzodiazepines but to confirm (or not) the relationship between benzodiazepine use and a delayed risk of dementia.
- As the exposure status was not considered during the 5 years preceding index date, the effect of the withdrawal or persistence of benzodiazepine use during this period was not evaluated. In any case, assessing the comparative effects of interrupting or not interrupting the treatment would have been tricky: withdrawal of the treatment can be as a result of the identification by the physician of a cognitive decline, while its persistence could be simply explained by the routine chronic use of benzodiazepines, which is quite prevalent among elderly.

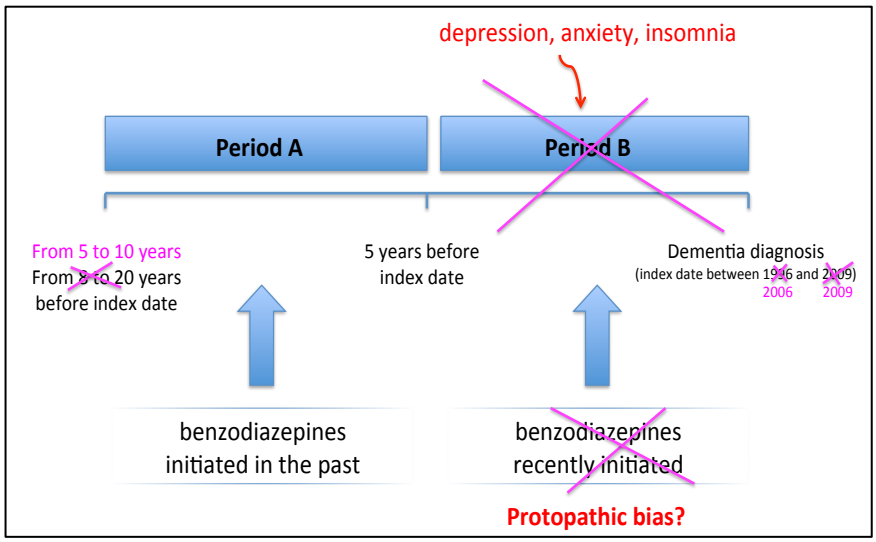


Figure X. The BENZODEM2 design contrasted with the BENZODEM case-control study

3.4.2.2. Sensitivity analysis

In order to take into account putative delays in the recording of the dementia diagnosis, we conducted a sensitivity analysis, the index date being pushed back one year to take into account a potential delay between the onset of disease and the recording of diagnosis in the RAMQ database. The exposure time-window then became the period between 6 and 10 years prior to diagnosis (index date).

3.4.3. Classification of exposure

Exposure was described according to three criteria:

3.4.3.1. Ever use

Ever use was defined as at least one benzodiazepine claim during the above-defined time-window. This simple and binary definition allowed for a global estimate of the effect of exposures initiated at least 5 years before index date and comparison with previous studies was made easier.

3.4.3.2. Cumulative dose

In the absence of an indisputable hypothesis about the possible involvement of a pathophysiological mechanism, the cumulative dose used was preferred since it combined both the duration of treatment and the somewhat variable daily dose. For each person and each product, the cumulative dose used during the study time-window was computed and then converted into a number of prescribed daily doses (PDDs) by dividing it by the average daily dose for this product in the source cohort.[171] Therefore, one PDD corresponded to an average one-day exposure. Three cumulative dose categories were considered:

(i) 1-90 PDDs (*i.e.* cumulative exposure ≤3 months),

(ii) 91-180 PDDs (3 to 6 months),

(iii)>180 PDDs (>6 months, long-term users).

<u>First note:</u> Prescribed Daily Dose was preferred to Defined Daily Dose for analyses

Defined Daily Dose (DDD) is the most common exposure measurement unit used in health statistics. It has been popularised by the World Health Organization (WHO) for comparing drug utilization across countries. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is mainly based on the dosage approved in the summary of product characteristics (SPC) and not on individual characteristics measured in a given population. Therefore, DDD may not reflect the dose used in a specific population since it should be considered as a compromise proposed by a panel of experts reviewing available information from various sources.

The Prescribed Daily Dose (PDD), on the other hand, is derived from the observation of real prescriptions. It is the averaged dose of a given medicinal product used in a given population. In most cases, for the same product, the PDD can vary according to:

- The illness treated,
- Country-specific therapeutic practices,
- Patient specificities (gender, age, body weight, inter-individual differences in drug metabolism, individual response to the drug).

For a given population, the number of prescribed daily doses is a much better indicator of the duration of exposure if the PDD was measured in this population or in a population with roughly the same characteristics.[171]

<u>Second note:</u> Some details about the PDD computation

(i) For each benzodiazepine molecule reimbursed, the unit dosage was converted into a number of milligrams of diazepam according to equivalences provided by the literature (Table 5).

(ii) For each participant, the cumulative dose (expressed in milligrams of diazepam) was computed for all molecules of benzodiazepine used during the observation period.

(iii) In order to derive the PDD value, the average daily dose of diazepam-equivalent used by benzodiazepine users was computed at the entry date in the RAMQ cohort.

(iv) For each subject, exposure density to benzodiazepines was expressed as the number of PDDs during the observation period, estimated by dividing the cumulative dose of diazepam reimbursed during the study period calculated in (ii) by the average dose of diazepam (PDD) calculated in (iii).

3.4.3.3. Drug elimination half-life

People were categorized as users of short- (<20 hours) or long-acting benzodiazepines. When different molecules were used by the same person, the longer half-life was retained (Table 23). This cut-off was chosen in accordance with current recommendations of good practices for prescription of benzodiazepines in the elderly. These recommendations suggest that molecules with short half-lives (<20h) should be preferred and that they should be prescribed for a limited period of time.

3.4.3.4. Reference group

People without any claim for benzodiazepines during the study time-window were categorized as non-users and served as reference for the analyses.

3.4.3.5. Summary of exposure classification

Exposure classification is summarised in Table 24.

Table 24. Classification of benzodiazepine exposure in BENZODEM2

EVER USE	DENSITY OF EXPOSURE (Prescribed Daily Doses, PDDs)	ELIMINATION HALF LIFE
At least one benzodiazepine claim	1 to 90* PDDs 91 to 180† PDDs >180‡ PDDs	short half-life (<20h) long half-life (≥20h)
Observation period: 5 to 10 years before the first diagnosis of Alzheimer's disease **Reference: no benzodiazepine claims during the observation period**		

* Use of the mean daily dose registered at the baseline of the exposed cohort for 3 cumulative months or less.
† Use of the mean daily dose registered at the baseline of the exposed cohort for 3 to 6 cumulative months.
‡ Use of the mean daily dose registered at the baseline of the exposed cohort for more than 6 cumulative months.

3.5. Covariates

Covariates other than those used for matching cases and controls, *i.e.* gender, age, follow-up duration, were measured during the same time-window as exposure to benzodiazepines (*i.e.* between 5 and up to 10 years prior to the index date in the main analysis and between 6 and up to 10 years prior to this date in the sensitivity analysis). Potential confounders have been chosen among the well-known risk factors for Alzheimer's disease (cf. Part I) and putatively associated with benzodiazepine prescription (cf. Part I) when information was available in the RAMQ

database.[86 117 150 151] Potential confounders included: high blood pressure (diagnosis based upon the following ICD-9 codes: 401.0, 401.1, 401.9, 402.0, 402.1, 402.9, 403.0, 403.1, 403.9, 404.0, 404.1, 404.9 or use of antihypertensive drug), myocardial infarction (ICD-9 codes: 410, 412), stroke (ICD-9 codes: 431, 432.0, 432.1, 432.9, 436, 437), use of platelet inhibitors or oral anticoagulants, hypercholesterolaemia (ICD-9 codes: 272.0 or use of lipid lowering drugs), diabetes mellitus (ICD-9 codes: 250 or use of antidiabetic drugs), anxiety (ICD-9 codes: 300.0, 300.2, 300.3), depression (ICD-9 codes: 296.2, 296.3, 300.4, 311), and insomnia (ICD-9 codes: 307.4, 327.3, 327.4, 780.5). Other diagnoses included those of the Charlson comorbidity index[172] validated for administrative claim databases:[173] chronic pulmonary disease, rheumatic disease, peptic ulcer, hemiplegia or paraplegia, renal disease, malignancy or metastatic solid tumour, liver disease, and AIDS/HIV. A broad category of "comorbidity" was created that included patients with at least one diagnostic claim for the above-listed diagnoses. The signification of ICD-9 codes used to defined comorbidities associated with benzodiazepine use and Alzheimer's disease are available in Annexes 4.

3.6. Analysis

The association between benzodiazepine use and dementia was assessed using multivariate conditional logistic regression considering the covariates listed above. At first, and as discussed in Part III, we did not include depression, anxiety, and insomnia in the model as the nature of their association with dementia (risk factor or prodrome) is under debate, and their *a priori* strong correlation with benzodiazepine exposure could result in an overadjustment (Model 1). Subsequently we added them to the model if they did not interact with exposure (Model 2).

4. Main results and interpretation

4.1. Population selection

We identified 1796 people as cases (Figure XI) and matched them with 7184 controls, both groups being followed up for at least six years before the index date.

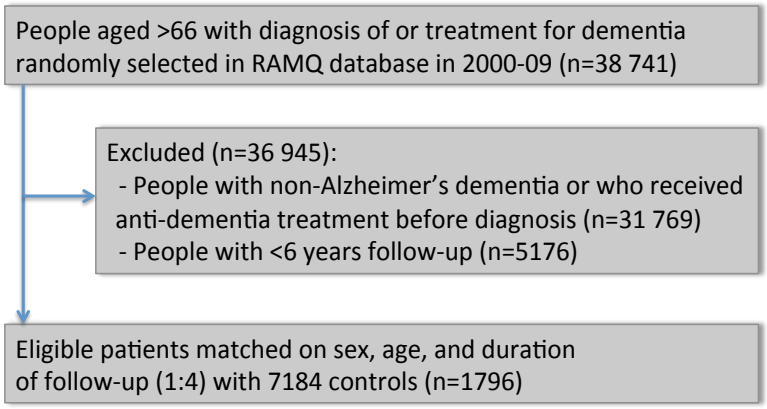


Figure XI. Selection of cases in the study on benzodiazepine use and the risk of Alzheimer's disease (Billioti de Gage *et al.*[149])

4.2. Cases and controls comparison

Characteristics of cases and controls included in the analyses are presented in Table 25. Compared to controls (n=7184), cases (n=1796) were more likely to have history of stroke (7% *versus* 6%), hypercholesterolaemia (21% *versus* 17%), anxiety (21% *versus* 15%) and less likely to have history of myocardial infarction (3% *versus* 5%). No differences were found for other covariates.

4.3. Association between benzodiazepine use and Alzheimer's disease

Ever use of benzodiazepines was found to be associated with an increased risk of Alzheimer's disease (adjusted odds ratio 1.51, 95% confidence interval 1.36 to 1.69). No difference was found for a cumulative dose corresponding to 1 to 90 days of use. For other users, the strength of association increased with density of exposure: 1.32 (1.01 to 1.74) for 91 to 180 PDDs and 1.84 (1.62 to 2.08) for more than 180 PDDs. The association was stronger for long-acting benzodiazepines (1.70 (1.46 to 1.98)) than for short-acting ones (1.43 (1.27 to 1.61)). (Table 26).

No significant interactions were found for anxiety, depression and insomnia and adjustment on these variables did not markedly alter the results. (Table 26).

Pushing back the index date by one year did not change the direction of the results. (cf. Annexes 4).

Table 25. Characteristics of subjects with Alzheimer's disease (cases) and controls (variables assessed five to up to 10 years before diagnosis). Figures are numbers (percentage) of subjects (Billioti de Gage *et al.*[149])

Characteristics	Cases n=1796 (%)	Controls n=7184 (%)	P value
Gender:			matched
Male	593 (33.0)	2372 (33.0)	
Female	1203 (67.0)	4812 (67.0)	
Age (years):			matched
70-74	239 (13.3)	956 (13.3)	
75-79	466 (26.0)	1864 (26.0)	
80-84	565 (31.5)	2260 (31.5)	
≥85	526 (29.3)	2104 (29.3)	
Follow-up (years):			matched
6	592 (33.0)	2368 (33.0)	
7	583 (32.5)	2332 (32.5)	
8	406 (22.6)	1624 (22.6)	
9	114 (6.3)	456 (6.3)	
10	101 (5.6)	404 (5.6)	
Benzodiazepine ever use:			<0.001
Non-users	902 (50.2)	4311 (60.0)	
Users	894 (49.8)	2873 (40.0)	
Benzodiazepine density exposure (number of prescribed daily doses):			<0.001
Non-users	902 (50.2)	4311 (60.0)	
1-90	234 (13.0)	1051 (14.6)	
91-180	70 (3.9)	257 (3.6)	
>180	590 (32.9)	1565 (21.8)	
Benzodiazepine elimination half-life:			<0.001
Non-users	902 (50.2)	4311 (60.0)	
Short half-life (<20h)	585 (32.6)	1996 (27.8)	
Long half-life (≥20h)	309 (17.2)	877 (12.2)	
High blood pressure*†	1155 (64.3)	4508 (62.8)	0.22
Myocardial infarction*	61 (3.4)	330 (4.6)	0.03
Stroke*	125 (7.0)	416 (5.8)	0.06
Hypercholesterolaemia*†	376 (20.9)	1187 (16.5)	$<10^{-3}$
Diabetes mellitus*†	336 (18.7)	1299 (18.1)	0.54
Comorbidity‡	719 (40.0)	2738 (38.1)	0.13
Platelet inhibitors or oral anticoagulants†	138 (7.7)	630 (8.8)	0.14
Anxiety*	384 (21.4)	1083 (15.1)	$<10^{-3}$
Depressive symptoms*	52 (2.9)	172 (2.4)	0.22
Insomnia*	72 (4.0)	229 (3.2)	0.08

*Evaluated by ICD-9 diagnosis.

†Evaluated by drug claims.

‡At least one medical ICD-9 diagnosis of chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, hemiplegia or paraplegia, renal disease, malignancy or metastatic solid tumor, HIV/AIDS, registered.

Table 26. Risk of Alzheimer's disease associated with benzodiazepine use (variables assessed 5 to up to 10 years before diagnosis) (Billioti de Gage *et al.*[149])

	Cases n=1796 (%)	Controls n=7184 (%)	Univariable odds ratio (95%CI)*	Multivariable odds ratio (95%CI)	
				Model 1*†	Model 2*‡
Benzodiazepine ever use:					
Non-users	902 (50.2)	4311 (60.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Users	894 (49.8)	2873 (40.0)	1.52 (1.37 to 1.69)	1.51 (1.36 to 1.69)	1.43 (1.28 to 1.60)
Benzodiazepine density exposure (number of prescribed daily doses):					
Non-users	902 (50.2)	4311 (60.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-90	234 (13.0)	1051 (14.6)	1.08 (0.92 to 1.27)	1.09 (0.92 to 1.28)	1.05 (0.89 to 1.24)
91-180	70 (3.9)	257 (3.6)	1.33 (1.01 to 1.75)	1.32 (1.01 to 1.74)	1.28 (0.97 to 1.69)
>180	590 (32.9)	1565 (21.8)	1.85 (1.63 to 2.09)	1.84 (1.62 to 2.08)	1.74 (1.53 to 1.98)
Benzodiazepine elimination half-life:					
Non-users	902 (50.2)	4311 (60.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Short half-life (<20h)	585 (32.6)	1996 (27.8)	1.43 (1.27 to 1.61)	1.43 (1.27 to 1.61)	1.37 (1.21 to 1.55)
Long half-life (≥20h)	309 (17.2)	877 (12.2)	1.72 (1.48 to 1.99)	1.70 (1.46 to 1.98)	1.59 (1.36 to 1.85)

*Matched for age, gender and follow-up length.
†Model 1: adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).
‡Model 2: Model 1 further adjusted for anxiety, depression and insomnia diagnosis.

5. Discussion

5.1. Main conclusions

This case-control study based on 8980 individuals representative of elderly people living in the community in Quebec showed that the risk of Alzheimer's disease was increased by 43 to 51% among those who had used benzodiazepines in the past. The risk increased with density of exposure and when long-acting benzodiazepines were used. Further adjustment on symptoms thought to be potential prodromes or risk factors for dementia, such as depression, anxiety or insomnia, did not meaningfully alter the results.

5.2. Strengths of the study

First, this study was specifically designed to minimise the possibility of a reverse causation. Exposure to benzodiazepines was compared across cases and controls on the basis of treatments initiated more than 5 years (6 in the sensitivity analysis) before the diagnosis of Alzheimer's disease, this period being less likely to convey a protopathic bias than more recent initiations. Moreover, a sensitivity analysis adjusting on potential prodromes of the disease did not alter the results, which adds a complementary argument against a prothopathic bias.
The study was also designed to assess a possible dose-effect relationship, a recognized argument for drug causation. In users of less than 90 PPDs, the risk of Alzheimer's disease did not differ

from controls, while it increased with the cumulative dose of exposure for users of more than 90 PDDs. The risk was higher, however, in users of long-acting benzodiazepines compared to users of short-acting ones, which is also an argument in favour of a dose-effect relationship.
Another strength of the study was that is was conducted on a large and representative sample, making the findings generalizable to the elderly population of Quebec.

5.3. Limitations of the study

This study shares the main limitations experienced with other studies conducted on reimbursement claims databases:

(i) Case ascertainment was made without direct access to the patient or his/her physician, which raises concern about a possible misclassification and delay between the actual date of onset of Alzheimer's disease and the date when it is recorded. The possibility of misclassification about the case or control status is described in the next part (see comment 1). To take into account the influence of a possible delay in recording the diagnosis of Alzheimer's disease, we pushed back the index date by one year in a sensitivity analysis (exposure was researched 6 years and more before the index date), which did not alter the results.

(ii) Ascertaining exposure status from what was recorded in a database always implies a degree of uncertainty about the congruence between the recorded date of benzodiazepine claims and the actual date of their consumption. Keeping in mind that a putative excess risk of dementia would only concern long-term treatments requiring multiple prescriptions, concern about poor compliance is not meaningful. It is therefore sensible to conclude that observed long-lasting uses actually corresponded to actual long-term exposures.

(iii) Several symptoms not considered as the main diagnoses could have been under-reported by the physicians. For example, this could be the case for neuropsychiatric symptoms considered for adjustment (depression anxiety, insomnia). This could result in a bias if this under-reporting was massive and/or not balanced among case and control groups.

(iv) No direct information about socioeconomic status, education level, smoking habits or alcohol consumption was available in the RAMQ database.

Despite these limitations, some of which being easily circumvented, the results of BENZODEM2 reinforced the arguments in favour of a direct link between benzodiazepine use and dementia, even if:

(i) A protopathic bias cannot be completely ruled out as an explanation of the association found, since the exact delay between the first prodromes and the appearance of a complete set of symptoms making the diagnosis of dementia clinically possible remains unknown.

(ii) Alternate hypotheses for explaining the association observed cannot be excluded. For example, anxiety and sleep disorders, two of the main indications for prescribing benzodiazepines, could be associated with early ß-amyloid lesions in the brain,[174 175] and persistent mid-life anxiety could be associated with a greater risk of dementia in older people. Therefore, benzodiazepine use might be an early marker of a condition associated with an increased risk of dementia and not the cause.

6. Complementary points

6.1. Reviewers' questions

Before publication by the British Medical Journal, numerous questions were addressed by the reviewers. We provide below a summary of the answers to their main comments.

6.1.1. About the diagnosis of Alzheimer's disease

Comment 1: The authors do not describe how a diagnosis of Alzheimer's disease has been reached amongst the cases.

In the RAMQ database, as for most other healthcare databases used for epidemiologic research, the diagnosis appears on billing claims filled by the physician on a fee-for-service basis. As in other developed countries, the diagnosis of dementia can be made by a general practitioner or by a specialist, *e.g.* a neurologist, an internist, or a geriatrician.

In the Quebec public drug plan, reimbursement for the initiation of a treatment with cholinesterase inhibitors is possible only for patients with an MMSE score ranging between 10 and 26. Furthermore, maintaining reimbursement after a treatment course of 6 months requires both (i) an absence of significant worsening (loss <3 in the MMSE score), and (ii) an improvement in at least one cognitive function. These reimbursement criteria (fulfilled for 72% of cases considered for analysis) clearly imply the repeated use of validated diagnostic tools. For

that reason, we believe that diagnosis misclassification and consequently the number of false-positives or false-negatives were not a major concern in this study. Moreover, as mentioned in the Discussion section of the manuscript, false-positives, if any, would have led to considering some subjects erroneously as cases and not as controls, and some false-negatives cases as controls. Such misclassification would tend to underestimate an exposure difference across cases and controls, if any, making the odds ratios more conservative.

Comment 2: The strength of diagnostic certainty is particularly important as the use of sedating medications such as benzodiazepines can impair cognition and confound a clinical diagnosis of dementia.

With the exception of some particular cases, it seems unlikely that the diagnosis of dementia was confounded by an effect of benzodiazepines on cognitive functions. Indeed:

(i) While the deleterious effect of benzodiazepines on memory is well-known, according to international guidelines such as DSM-IV,[14] [144] the diagnosis of dementia requires concurrent impairment of at least one of the following domains: reasoning and handling of a complex task, visuospatial abilities, language functions.

(ii) A review of the existing literature does not support a deleterious *a fortiori* delayed effect of benzodiazepines on cognitive functions.[124] [176] [177]

(iii) Such effects, if pharmacologically mediated, may be expected to occur once the maximal concentrations of benzodiazepines and active metabolites in the brain are reached, *i.e.* after some days or weeks. Therefore, it is unlikely that such effects would induce a first diagnosis of dementia more than 5 years after treatment initiation.

(iv) We provide below adjusted odds ratios for the effects of benzodiazepine treatments that are still active on the date of the dementia diagnosis, as well as odds ratios for those that were discontinued at least one year before. The results for the most relevant exposure category, *i.e.* >6 months, clearly do not support any association that could be explained by the central nervous system effects of active concentrations of benzodiazepines:

- Active treatment: OR 1.72 (1.51 to 1.97),
- Discontinued at least one year before: OR 2.51 (1.97 to 3.20).

The results of other categories are provided in Table 27 and are in accordance with those found for the most relevant exposure category.

Table 27. Effects of benzodiazepine treatments still active on the date of the dementia diagnosis and discontinued at least one year before (variables assessed 5 to up to 10 years before diagnosis)

Benzodiazepine density exposure (PDDs), active or discontinued	Cases n=1796 (%)	Controls n=7184 (%)	Univariable odds ratio (95% CI)*	Multivariable odds ratio (95%CI)	
				Model 1*†	Model 2*‡
Non-users	902 (50.2)	4311 (60.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-90, active	68 (3.8)	229 (3.2)	1.44 (1.09 to 1.92)	1.43 (1.07 to 1.91)	1.38 (1.04 to 1.84)
1-90, discontinued	166 (9.2)	822 (11.4)	0.98 (0.82 to 1.18)	0.98 (0.82 to 1.18)	0.95 (0.79 to 1.15)
91-180, active	35 (2.0)	170 (2.4)	1.01 (0.69 to 1.46)	1.00 (0.69 to 1.45)	0.96 (0.66 to 1.39)
91-180, discontinued	35 (2.0)	87 (1.2)	1.94 (1.31 to 2.90)	1.94 (1.30 to 2.90)	1.90 (1.27 to 2.84)
>180, active	476 (26.5)	1342 (18.7)	1.74 (1.52 to 1.98)	1.72 (1.51 to 1.97)	1.63 (1.43 to 1.87)
>180, discontinued	114 (6.4)	223 (3.1)	2.49 (1.96 to 3.16)	2.51 (1.97 to 3.20)	2.35 (1.84 to 3.01)

*Matched for age, gender and follow-up duration.
†Model 1: adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).
‡Model 2: Model 1 with supplementary adjustment for anxiety, depression and insomnia diagnosis.

6.1.2. About reverse causality bias

Comment 3: Assessing benzodiazepine treatments initiated more than 5 years prior to diagnosis is insufficient to exclude reverse causation as prodromal symptoms of Alzheimer's have been identified up to 12 years prior to a formal diagnosis (e.g. Helene Amieva et al. Annals of Neurology 64(5) 492-498 Nov 2008).[19]

We have attempted to reduce bias due to reverse causation by using various methods of data analyses and restriction. However, we agree with the reviewer that reversed causality cannot be excluded as alternative explanation of the findings. Nevertheless, we believe that the likelihood that the results are mainly driven by reversed causation is low.

For prodromal symptoms, the literature findings confirm, despite somewhat contradictory results, that a higher prevalence of anxiety, depression or sleep disorders may be observed in the years preceding the diagnosis of Mild Cognitive Impairment (MCI) or dementia. Sadly, the length of follow-up in these studies is often too short to derive a precise time of onset of these symptoms. Amieva's paper[19] from 2008 did not explore anxiety or sleep disorders but changes in the CES-D scale. When considering this score as a continuous variable and not as a dichotomous variable, *i.e.* depressed or not depressed, the scores were significantly higher 7 to 8 years before the diagnosis of dementia but, surprisingly, without further worsening.

In the present paper, the association between dementia and benzodiazepines persisted after adjustment for anxiety, depression and sleep disorders, and was not altered when analysis was performed 6 years rather than 5 years before diagnosis. Moreover, most of the exposed cases had initiated their treatment much longer than 5 years before dementia diagnosis. Indeed, at the time of inclusion in the study, 85% of cases and 80% of controls were prevalent users of benzodiazepines.

Comment 4: The main weakness of the study, however, is that it still does not answer the question of causality. The easiest way the authors could have addressed this issue, and this is suggested, would be to use another comparison group of mood stabilizers used in the treatment of depression, insomnia, and anxiety (such as tricyclic antidepressants, tetracyclic antidepressants, SSRIs, SNRIs etc.).

The causal nature of the association found between benzodiazepines and dementia remains debatable. This is more often than not the case in non-experimental studies, even when extensive efforts have been made to minimise reverse causality. Such efforts consisted of the following: (i) only treatments initiated 5 or 6 years before diagnosis were considered, (ii) further adjustment was made for symptoms that are both potential prodromes and indications for prescribing benzodiazepines, and (iii) a dose-response relationship was investigated.
In that sense, using another comparison group of mood stabilizers such as antidepressants as the benchmark is interesting, even if some of these drugs could be suspected of deleterious effects on cognitive functions as a result of their marked anticholinergic properties.
In the present case, such an analysis was not statistically valid since:

- Use of antidepressants was strongly correlated with use of benzodiazepines: among cases, 75.7% of users of antidepressants were also using benzodiazepines, and this percentage was 70.4% among controls.
- Consequently, this comparison group would be undersized (users of antidepressant alone would account for 5.9% of cases and 4.8% of controls) compared to the study group and would probably not be representative of patients with depression.

Moreover, another concern arose about the validity of such a reference group in the present context: (i) some of these drugs could be suspected of deleterious effects on cognitive functions as a result of their marked anticholinergic properties (*e.g.* imipramine and related compounds), (ii) if depression was actually a risk factor for dementia it is sensible to assume that for a certain number of patients (mainly those having started to be treated before the prodromal phase) antidepressants, if effective against depression, could have a protective effect. Consequently, using antidepressant users as a reference could be suspect of leading to erroneous estimates.
As an alternative to the Reviewer's suggestion, *e.g.* to neutralize the modifying effect of antidepressants or of conditions associated with their use, we have assessed the strength of the association with dementia in benzodiazepine users who were not using or had not used antidepressants during the study time-window, adjustment being made as in the main analysis. The risk of Alzheimer's disease increased by about 36% in benzodiazepine users with a dose-effect relationship, and a slight effect of the elimination half-life of the molecule, see Annexes 4).

6.1.3. About exposure definition

Comment 5: In general the methods are clearly described. However the description of Prescribed Daily Dose (PDD) calculation is difficult to follow and also whether they have considered variable daily dosing regimens.

PDDs were used precisely in order to take into account putative variations in daily dosing regimens since they are computed by totalling the doses, variable or not, of each product used by each subject. The same choice was made by Weich and colleagues in their 2014 BMJ paper on benzodiazepines and global mortality.[178] Performing the analyses by using the actual cumulative number of days of exposure led to similar results:

- ≤90 days: OR 1.01 (0.85 to 1.20),
- 91 to 180 days: OR 1.47 (1.12 to 1.94),
- 180 days: OR 1.81 (1.61 to 2.05).

The results of analyses using cumulative days of exposure are provided in Table 28.

Table 28. Estimation of the relation between benzodiazepine use and Alzheimer's disease. Results of analysis using cumulative days of exposure compared to the results of analysis using cumulative doses (variables assessed 5 to up to 10 years before diagnosis)

	Cases	Controls	Univariable odds	Multivariable odds ratio (95%CI)	
	n=1796 (%)	n=7184 (%)	ratio*	Model 1*†	Model 2*‡
Benzodiazepine density exposure (number of Prescribed Daily Doses):					
Non-users	902 (50.2)	4311 (60.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1 to 90	234 (13.0)	1051 (14.6)	1.08 (0.92 to 1.27)	1.09 (0.92 to 1.28)	1.05 (0.89 to 1.24)
91 to 179	70 (3.9)	257 (3.6)	1.33 (1.01 to 1.75)	1.32 (1.01 to 1.74)	1.28 (0.97 to 1.69)
>180	590 (32.9)	1565 (21.8)	1.85 (1.63 to 2.09)	1.84 (1.62 to 2.08)	1.74 (1.53 to 1.98)
Benzodiazepine length of exposure (number of cumulative days):					
Non-users	902 (50.2)	4311 (60.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-90	200 (11.1)	969 (13.5)	1.01 (0.85 to 1.19)	1.01 (0.85 to 1.20)	0.97 (0.82 to 1.15)
91-180	71 (4.0)	232 (3.2)	1.47 (1.12 to 1.94)	1.47 (1.12 to 1.94)	1.41 (1.06 to 1.86)
>180	623 (34.7)	1672 (23.3)	1.83 (1.62 to 2.06)	1.81 (1.61 to 2.05)	1.72 (1.51 to 1.95)

*Matched for age, gender and follow-up duration.
†Model 1: adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).
‡Model 2: Model 1 with supplementary adjustment for anxiety, depression and insomnia diagnosis.

Comment 6: It is also not clear whether when segregating benzodiazepines in terms of drug elimination half-life they have considered the number of daily doses for each subject which will also affect drug clearance.

The odds ratios provided for comparing short- and long-acting benzodiazepines concerned ever

exposure. Owing to the restriction in the length of the manuscript and number of results that may be presented, the two groups of substances were not compared for different amounts of cumulative daily doses.

The use of higher daily doses than those recommended can progressively lead to high brain concentrations, mainly for long-acting substances.

For example, comparing short- and long-acting substances for >180 PDD exposures, *i.e.* the most relevant scheme for the Reviewer's remark, yields the following results:

- Short-acting: OR 1.74 (1.51 to 2.02),
- Long-acting: OR 2.00 (1.69 to 2.38).

All the results are given in Table 29.

Table 29. Estimation of the relation between benzodiazepine use and Alzheimer's disease. Results of analysis considering both cumulative doses and half-lives of the molecules (variables assessed 5 to up to 10 years before diagnosis)

Benzodiazepine density exposure (PDDs), elimination half-life	Cases (n=1796)	Controls (n=7184)	Univariable odds ratio (95% CI)*	Multivariable odds ratio (IC95%)	
				Model 1*†	Model 2*‡
Non-exposed	902 (50.2)	4311 (60.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-90, short	180 (10.0)	813 (11.3)	1.08 (0.90 to 1.29)	1.08 (0.90 to 1.30)	1.05 (0.88 to 1.26)
1-90, long or mixed	54 (3.0)	238 (3.3)	1.09 (0.81 to 1.49)	1.09 (0.80 to 1.48)	1.05 (0.77 to 1.42)
91-180, short	48 (2.7)	181 (2.5)	1.30 (0.94 to 1.80)	1.28 (0.92 to 1.78)	1.24 (0.89 to 1.73)
91-180, long or mixed	22 (1.2)	76 (1.1)	1.40 (0.87 to 2.27)	1.42 (0.88 to 2.30)	1.37 (0.85 to 2.22)
>180, short	357 (19.9)	1002 (14.0)	1.75 (1.51 to 2.02)	1.74 (1.51 to 2.02)	1.67 (1.44 to 1.93)
>180, long or mixed	233 (13.0)	563 (7.8)	2.02 (1.71 to 2.40)	2.00 (1.69 to 2.38)	1.87 (1.56 to 2.23)

*Matched for age, gender and follow-up duration.

†Model 1: adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).

‡Model 2: Model 1 with supplementary adjustment for anxiety, depression and insomnia diagnosis.

6.2. Supplementary research

To reply to several comments, we performed a series of complementary analyses to estimate the influence of other psychotropics on the probability of dementia. The methodology used and the results are presented in our special topic (Part V, section 3).

7. Summary, conclusion and other questions

In this case-control study conducted on the Quebec database claims we underlined:

- A statistically significant increased risk (OR 1.3 to 1.8) of dementia in subjects who had used more than 90 PDDs of benzodiazepines (which corresponded to at least 3 months of use at usual daily dose),

- A clear dose-effect relationship (the strength of association markedly increased with density of exposure: OR about 1.3 for 91 to 180 PDDs, and about 1.7 to 1.8 for more than 180 PDDs).

- A greater risk when using long-acting benzodiazepines compared to short-acting ones (OR about 1.6 to 1.7 and 1.4, respectively).

These results confirm those of the PAQUID programme: the association that we found, (1) had the same direction and the same strength, and (2) seemed not predominantly explained by a protopathic bias. Compared to the studies conducted in the PAQUID cohort, the Quebec database study added a supplementary argument for a possible causal association: a dose effect relationship.

While this study made it possible to clarify several points left unresolved at the end of the BENZODEM/PAQUID programme (*i.e.* influence of the dose, type of molecule, adjustment on other prodromes of the disease: anxiety and insomnia), the mechanism explaining the relationship between benzodiazepine use and dementia remains unclear.

The case-controls study conducted on the Quebec database claims led to a publication in the British Medical Journal in September 2014.[179]

PART V - Additional topics

1. Presentation

In the context of our main objective (*i.e.* to assess the relationship between benzodiazepine use and dementia), several pending issues or complementary questions led us to conduct supplementary studies and analyses. Just before publication of the BENZODEM study (cf. Part III), an article reported a 3- to 5-fold increase in the risk of global mortality in users of hypnotics.[180] This reinforced our concern (as most of hypnotics are benzodiazepines) about a possible limitation of our studies as they did not sufficiently take into account the putative effect of mortality as a competing risk in estimating the relationship between benzodiazepines and dementia (cf. subsection 2). We were also concerned by the possible modifying effect of the use of other psychotropics on the relationship between benzodiazepines and dementia, as these drugs are often co-prescribed with benzodiazepines and some of them could also have deleterious effects on cognition (*e.g.* anticholinergic effects of antipsychotics and antidepressants). This concern had led to a preliminary work, not presented in the final version of the article (cf. subsection 3). After the publication of the BENZODEM studies, we tried to explore various hypotheses about the putative biological mechanism which would explain the results (cf. subsection 4). Finally, we tried to better understand the patterns of benzodiazepine consumption and their evolution over time (cf. subsection 5).

2. Benzodiazepines and the risk of dementia: taking mortality into account

2.1. Competing mortality risk

2.1.1. Context and objectives

Before the publication of the BENZODEM results, we were concerned by the fact that attrition due to mortality could be a possible source of bias when assessing the relation between benzodiazepines and dementia. Indeed, mortality occurring before the end of the follow-up could introduce differential attrition, leading to an overestimation of the incidence of the event in one group (dying prevents a long follow-up, and thus decreases the probability of developing dementia). Competing risk may typically affect cohort studies, mainly when the follow-up is long and the incidence of the competing risk is higher than that of the outcome studied. The problem may occur when attrition due to the competing risk, in the present case death from all causes, affects the groups compared unequally, leading to a spurious difference in the incidence rates of the outcome.

In the framework of BENZODEM, this eventuality was not theoretical since the follow-up was long and the age at inclusion was high. In the publication of the BENZODEM programme we did not clearly demonstrate that our results were not, at least in part, affected by such a competing risk. We therefore conducted a cohort study in order to evaluate the influence of a putative differential mortality rate on the estimates.

2.1.2. Method

We performed a new survival analysis using the same sample as described in the main prospective approach of the BENZODEM programme (Part III). The same definitions were used for both exposure to benzodiazepines (*i.e.* new-initiation at the fifth year following inclusion in the PAQUID cohort, T_5) and dementia (*i.e.* incident cases after T_5). After a literature search and having compared the different options, we chose the Fine and Gray model[181] typically developed for competing risk analysis and enabling us: (i) to correct incidence estimates and cumulative incidence curves, and (ii) to provide corrected estimates (corrected Hazard Ratios, HR). The basic principle of competing risk analysis is that dead people continue to be considered in the risk sample for survival analysis after their death, their weight in the model decreasing during the follow-up as events of interest occur. This model compensates for the effect of attrition due to the competing risk.

2.1.3. Results

As shown in Figure XII, the excess risk of dementia in the exposed group appeared delayed by more than 5 years since benzodiazepine initiation in the corrected cumulative incidence curve, as was the case in the original survival curve in the BENZODEM/PAQUID study (Part III). After taking mortality into account, the Fine and Gray model gave the following corrected estimate: adjusted HR for dementia in new users of benzodiazepines 1.55, 95%CI 1.04 to 2.32, which was very similar to the estimate reported in BENZODEM (*i.e.* HR 1.62, 95%CI 1.08 to 2.43).

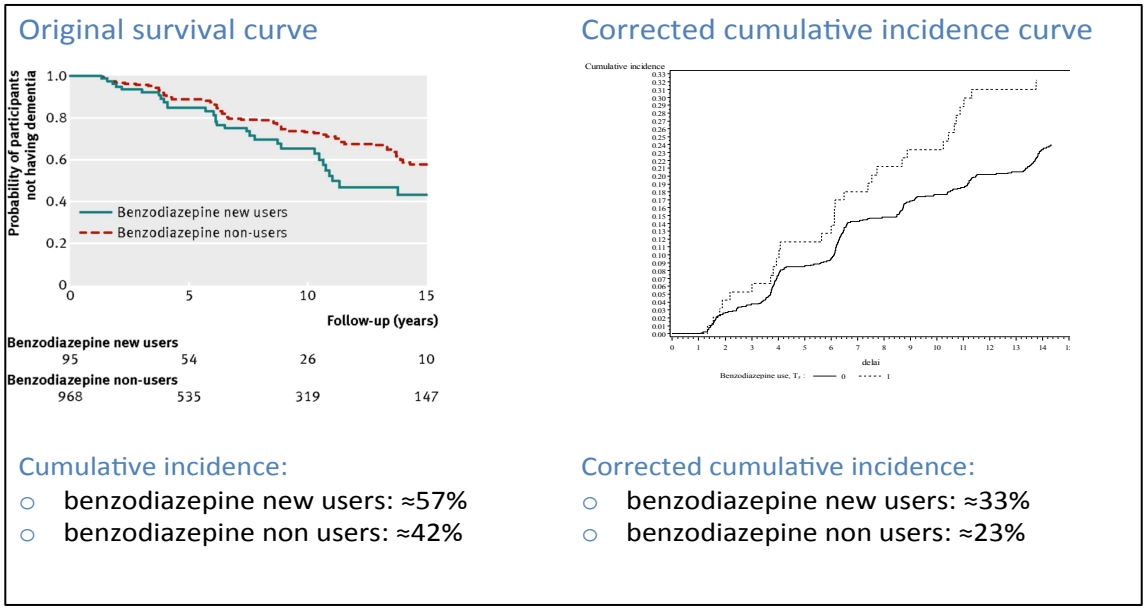


Figure XII. Comparison between BENZODEM original survival curve (Kaplan Meier) and cumulative incidence curve corrected for mortality as competing risk (Fine and Gray)

2.1.4. Discussing competing mortality risk

Taking possible competing mortality into account led to similar results to traditional event-free survival analysis. This could at first seem surprising as a recent study reported a differential mortality in benzodiazepine users compared to non-users.[180] Several hypotheses could explain this apparently paradoxical finding:

(1) There was no competing risk between mortality and dementia and no other analyses were needed. This seems unlikely since the prevalence of death was expected to be high in this elderly population. Moreover, the cumulative incidence of dementia was slightly weaker after taking mortality into account (Figure VII).

(2) Our study sample had an abnormally low risk of death or an abnormally high risk of dementia, making the effect of competition negligible. This was not realistic since PAQUID is known to be representative of the elderly general population.[147]

(3) There actually was a competing effect of death but it was equally balanced across the groups compared and, consequently, had no any influence on the estimates. This would lead to the question: is there actually an increased risk of mortality in benzodiazepine users as stated by the recent study?[180]

2.2. Benzodiazepines and mortality

2.2.1. Context and objective

As studies having assessed the risk of mortality associated with benzodiazepine use provided inconsistent findings, the possibility of biases remained debatable.[178 182 183] We therefore aimed to assess the reality of an increased mortality risk in elderly users of benzodiazepines. Non-differential mortality between exposed and non-exposed groups would confirm the last hypothesis (cf. (3) in subsection 2.1.4) and would explain the absence of competing risk between mortality and dementia.

2.2.2. Method

We performed a prospective study within the PAQUID cohort. We first compared prevalent users of benzodiazepines to non-users at inclusion in the PAQUID programme regarding a subsequent risk of mortality. Next, we made the same comparison between incident users of benzodiazepines and never users at the first time point (*i.e.* 3 years after inclusion, T_3). Subgroup analyses of benzodiazepine users were conducted in order to evaluate a putative effect of the molecule elimination half-life (long, *i.e.* ≥20 h or short). A Cox model adjusted on the main putative confounders measured at inclusion (T_0) in the PAQUID programme (*i.e.* age, gender, education level, singleness, several variables associated with cardiovascular risk, MMSE, perceived health) was used to estimate the Hazard Ratios (HRs) for mortality between groups. A sensitivity analysis considered a supplementary adjustment on depressive disorders and the use of other psychotropics, both highly linked with benzodiazepine use at the expense of a possible colinearity between variables.

2.2.3. Results

2.2.3.1. Comparison of exposed and non-exposed

Compared to non-users of benzodiazepines at inclusion in PAQUID, prevalent users were more often female, aged ≥75 years, with a lower schooling level, worse perceived health, living alone, using other psychotropics, having depressive disorders, cardio- or cerebrovascular comorbidities, a lower MMSE score, but were less often wine consumers or smokers. Compared to non-users, incident users of benzodiazepines were more often female, ≥75 years, with a

worse perceived health, they used other psychotropics more often and had cardio- or cerebrovascular comorbidities and depressive disorders more often (cf. Table 30).

Table 30. Comparison between characteristics of users (prevalent or incident) and non-users in the PAQUID cohort at inclusion

	Prevalent use at T_0			Incident use at T_3		
	Yes, n=1212 (%)	**No, n=2565 (%)**	**P value**	**Yes, n=221 (%)**	**No, n=1453 (%)***	**P value**
Death	1002 (82.7)	2036 (79.4)	0.02	182 (82.4)	1087 (74.8)	0.01
Female	877 (72.4)	1323 (51.6)	$<10^{-4}$	134 (60.6)	740 (50.9)	<0.01
Age (years):			0.03			<0.01
65-69	317 (26.2)	770 (30.0)		51 (23.1)	491 (33.8)	
70-74	252 (20.8)	556 (21.7)		56 (25.3)	323 (22.2)	
75-79	322 (26.6)	597 (23.3)		67 (30.3)	332 (22.9)	
>80	321 (26.5)	642 (25.0)		47 (21.3)	307 (21.1)	
Schooling duration (years):			$<10^{-4}$			0.08
<7	493 (40.7)	849 (33.1)		64 (29.0)	412 (28.4)	
7-9	528 (43.6)	1110 (43.3)		112 (50.7)	647 (44.5)	
>9	191 (15.8)	606 (23.6)		45 (20.4)	394 (27.1)	
Single	469 (38.7)	770 (30.0)	$<10^{-4}$	71 (32.1)	436 (30.0)	0.52
Perceived health:			$<10^{-4}$			$<10^{-4}$
Good	358 (29.5)	1409 (54.9)		104 (47.1)	887 (61.1)	
Medium	643 (53.1)	944 (36.8)		83 (37.6)	492 (33.9)	
Bad	204 (16.8)	196 (7.6)		32 (14.5)	68 (4.7)	
missing values	7 (0.6)	16 (0.6)		2 (0.9)	6 (0.4)	
High blood pressure	785 (64.8)	1328 (51.8)	$<10^{-4}$	120 (54.3)	726 (50.0)	0.23
Hypercholesterolemia	119 (9.8)	269 (10.5)	0.53	34 (15.4)	149 (10.3)	0.02
Diabetes	106 (8.8)	210 (8.2)	0.56	14 (6.3)	114 (7.9)	0.43
Wine consumption:			$<10^{-4}$			0.06
No	616 (50.8)	1036 (40.4)		105 (47.5)	571(39.3)	
Yes	594 (19.0)	1521 (59.3)		116 (52.5)	880 (60.6)	
missing values	2 (0.2)	8 (0.3)		0 (0.0)	2 (0.1)	
Tobacco use:			$<10^{-4}$			0.34
No	863 (71.2)	1524 (59.4)		143 (64.7)	869 (59.8)	
yes (current or previous)	347 (28.6)	1036 (40.9)		78 (35.3)	582 (40.1)	
missing values	2 (0.2)	5 (0.2)		0 (0.0)	2 (0.1)	
MMSE:			$<10^{-4}$			0.09
<24	343 (28.3)	551 (21.5)		47 (21.3)	243 (16.7)	
24-27	460 (38.0)	885 (34.5)		71 (32.1)	495 (34.1)	
>27	380 (31.4)	1063 (41.4)		97 (43.9)	698 (48.0)	
missing values	29 (2.4)	66 (2.6)		6 (2.7)	17 (1.2)	
Cardio or cerebrovascular comorbidities†:			$<10^{-4}$			<0.01
No	720 (59.4)	1790 (69.8)		136 (61.5)	1047 (72.1)	
Yes	486 (40.1)	766 (29.9)		85 (38.5)	400 (27.5)	
missing values	6 (0.5)	9 (0.4)		0 (0.0)	6 (0.4)	
Depressive symptoms:			$<10^{-4}$			$<10^{-3}$
No	895 (73.8)	2258 (88.0)		185 (83.7)	1030 (91.5)	
Yes	277 (22.9)	229 (8.9)		30 (13.6)	95 (6.5)	
missing values	40 (3.3)	78 (3.0)		6 (2.7)	28 (1.9)	
Other psychotropic use (at T_0 or T_3)	237 (19.6)	192 (7.5)	$<10^{-4}$	57 (25.8)	152 (10.5)	$<10^{-4}$

*Non-users at T_0 and T_3.

†Ischemic heart diseases (angina, history of myocardial infarction), or aftermaths of stroke, or use of anticoagulants or platelet inhibitors, or use of coronary vasodilators.

2.2.3.2. Survival curves

Figure XIII shows the Kaplan Meier curves comparing probabilities of survival between benzodiazepine users (prevalent or incident) and non-users according to time.

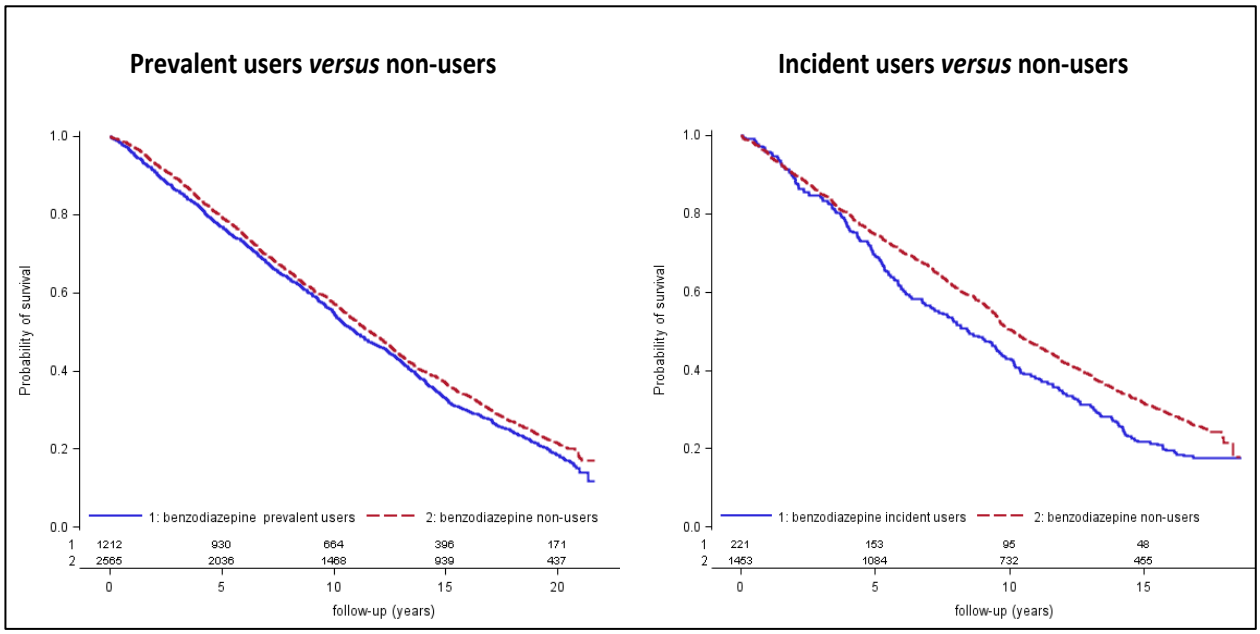


Figure XIII. Survival curves of benzodiazepine users (prevalent or incident) *versus* non-users

2.2.3.3. Association between exposure and mortality

During the 20-year follow-up, 1002 (82.7%) deaths were confirmed among subjects using benzodiazepines at inclusion (prevalent users) and 2036 (79.4%) among non-users at this date. During the 17-year follow-up, 182 (82.4%) deaths were confirmed among incident users of benzodiazepines at T_3 and 1087 (74.8%) among non-users at this date. Prevalent use of benzodiazepines was not associated with an excess risk of mortality (HR 0.99, 95%CI 0.91 to 1.07) in the model adjusted on the above-mentioned covariates. The same conclusion was true for incident use of benzodiazepines (1.12 (0.94 to 1.32)) in the model adjusted on the same covariates. These conclusions remained unchanged when considering the use of long- or short-acting molecules (Table 31, for prevalent use and Table 32, for incident use).

Table 31. Association between benzodiazepine prevalent use and mortality, PAQUID programme

Benzodiazepine prevalent use	Hazard ratio (95%CI) age, gender adjusted, n=3777	Multivariable hazard ratio (95%CI), n=3742		
		Model 1*	Model 2†	Model 3‡
Non-users	1.00 (reference) n=2565, deaths=2036	1.00 (reference) n=2535, deaths=2007	1.00 (reference) n=2535, deaths=2007	1.00 (reference) n=2535, deaths=2007
Prevalent users at T_0 (long or short half-life)	1.16 (1.07 to 1.25) n=1212, deaths=1002	1.00 (0.92 to 1.08) n=1196, deaths=986	0.99 (0.91 to 1.08) n=1196, deaths=986	0.99 (0.91 to 1.07) n=1196, deaths=986
Prevalent users at T_0 (long half-life)	1.10 (0.98 to 1.23) n=443, deaths=362	0.93 (0.82 to 1.04) n=437, deaths=356	0.93 (0.83 to 1.04) n=437, deaths=356	0.92 (0.82 to 1.04) n=437, deaths=356
Prevalent users at T_0 (short half-life)	1.19 (1.09 to 1.30) n=768, deaths=639	1.04 (0.95 to 1.15) n=758, deaths=629	1.03 (0.94 to 1.13) n=758, deaths=629	1.02 (0.93 to 1.12) n=758, deaths=629

*Model 1: adjusted for age, gender, living alone, education, self-perceived health, hypertension, hypercholesterolaemia, diabetes, cardiovascular or cerebrovascular problems, wine consumption, smoking and Mini-Mental State Examination score at T_0.
† Model 2: Model 1 further adjusted for depression at T_0.
‡ Model 3: Model 2 further adjusted for psychotropic use (other than benzodiazepines) at T_0.

Table 32. Association between benzodiazepine incident use and mortality, PAQUID programme

Benzodiazepine incident use	Hazard ratio (95%CI) age, gender adjusted, n=1674	Multivariable hazard ratio (95%CI), n=1612		
		Model 1*	Model 2†	Model 3‡
Non-users	1.00 (reference) n=1453, deaths=1087	1.00 (reference) n=1403, deaths=1041	1.00 (reference) n=1403, deaths=1041	1.00 (reference) n=1403, deaths=1041
New users at T_3 (long or short half-life)	1.23 (1.05-1.44) n=221, deaths=182	1.17 (0.99-1.38) n=209, deaths=171	1.17 (0.99-1.38) n=209, deaths=171	1.12 (0.94-1.32) n=209, deaths=171
New users at T_3 (long half-life)	1.15 (0.85-1.54) n=55, deaths=45	1.11 (0.81-1.52) n=52, deaths=42	1.11 (0.81-1.51) n=52, deaths=42	1.07 (0.77-1.45) n=52, deaths=42
New users at T_3 (short half-life)	1.25 (1.05-1.50) n=166, deaths=137	1.18 (0.98-1.43) n=157, deaths=129	1.19 (0.98-1.43) n=157, deaths=129	1.13 (0.93-1.36) n=157, deaths=129

*Model 1: adjusted for age, gender, living alone, education, self perceived health, hypertension, hypercholesterolaemia, diabetes, cardiovascular or cerebrovascular problems, wine consumption, smoking and Mini-Mental State Examination score at T_0.
†Model 2: Model 1 further adjusted for depression at T_0.
‡Model 3: Model 2 further adjusted for psychotropic use (other than benzodiazepines) at T_0 or T_3.

2.2.4. Conclusion about the association between benzodiazepine and mortality

We found no association between benzodiazepine use and an increased risk of mortality whatever the definition considered for exposure (prevalent or incident use, use of long- or short-acting molecule). These results were congruent with the fact that in the Fine and Gray model the association between benzodiazepine use and dementia was not modified when considering the putative competing effect of mortality.

2.3. What would happen in the event of differential attrition due to death between comparison groups?

Finally, we wondered how the association between benzodiazepines and dementia found in the main prospective BENZODEM study could have been modified in the event of a differential

mortality between the groups compared. The Hazard Ratios (HRs) were 1.62 (95%CI 1.08 to 2.43) when ignoring a putative competing risk of mortality, and 1.55 (1.04 to 2.32) when considering this risk (see 2.1.3). The adjusted HR for death estimated between comparison groups (*i.e.* 95 incident users of benzodiazepines and 968 non-users at the reference date T_5) was 1.12 (0.82 to 1.50) indicating no potential for a competing bias, or only a negligible one. The effect of a potential competing risk of death was then studied by modifying the death onset delay in subjects who died during the follow-up. This was first shortened by 5 to 50% in the benzodiazepine new users group in order to artificially increase the imbalance in the risk of death between groups by making it greater in exposed subjects. The same process was then applied for benzodiazepine non-users, while returning to the actual date of death in new users in order to increase the imbalance in the risk of death at the expense of non-exposed subjects. When shortening the death onset delay by 20% and 50% in benzodiazepine initiators, adjusted HRs estimated using a competing risk model were 1.72 (1.17 to 2.52), and 2.08 (1.42 to 3.04), respectively (Table 33). Conversely, when shortening the death onset delay by 20% and 50% in benzodiazepine non-users, adjusted HRs for dementia were 1.36 (0.93 to 2.00), and 1.13 (0.77 to 1.66), respectively (Table 33). These results illustrated the potential influence of competing risk on the estimates.

Table 33. Association between benzodiazepine use and death and benzodiazepines and dementia under several simulations of excess mortality in benzodiazepine users and non-users

	Death hazard ratio for new users (95%CI)*	Dementia hazard ratio for new users (95%CI)†
Initial situation	1.12 (0.82 to 1.50)	1.55 (1.04 to 2.32)
Death onset shortening in benzodiazepine initiators (%):		
5	1.15 (0.86 to 1.54)	1.55 (1.06 to 2.27)
10	1.18 (0.88 to 1.58)	1.62 (1.10 to 2.37)
20	1.25 (0.09 to 1.67)	1.72 (1.17 to 2.52)
50	1.49 (1.11 to 2.00)	2.08 (1.42 to 3.04)
Death onset shortening in benzodiazepine non-users (%):		
5	1.08 (0.80 to 1.44)	1.48 (1.01 to 2.17)
10	1.04 (0.78 to 1.40)	1.44 (0.99 to 2.11)
20	0.98 (0.73 to 1.32)	1.36 (0.93 to 2.00)
50	0.86 (0.64 to 1.15)	1.13 (0.77 to 1.66)

*Adjusted for age, gender, living alone, education, self-perceived health, hypertension, hypercholesterolaemia, diabetes, cardiovascular or cerebrovascular problems, wine consumption, smoking and Mini-Mental State Examination score at T_0.
†Model taking into account competing mortality, adjusted for age, sex, schooling duration, singleness, wine consumption, use of antihypertensive drugs, use of antidiabetic agents, use of statins, use of platelet inhibitors or oral anticoagulants, depressive symptoms measured at T_5 and Mini-Mental State Examination evolution between inclusion (T_0) and three-year follow-up visit (T_5).

2.4. Conclusion about the role mortality

Mortality, considered as a potential competing event, did not distort the estimates of the relationship between benzodiazepines and dementia since no differential mortality between exposed and non-exposed was observed. Simulations considering various hypotheses of differential mortality across groups led to significant changes in the original estimates. Consequently, when a competing event is likely to influence the duration of follow-up, it should be considered (competing risk) and its influence neutralised. This is particularly true for mortality risk, which should be systematically checked in pharmacoepidemiological studies conducted among elderly populations. The abstracts of two manuscripts currently in submission process (Benzodiazepines and mortality and competing risks: why should we care in pharmacoepidemiology research? And Global mortality associated with benzodiazepine use) are available in Annexes 1.

3. Other psychotropic use and dementia

3.1. Was the relation between benzodiazepine use and dementia modified by the use of other psychotropics?

3.1.1. Context and objectives

The possible modifying effect of the relationship found between benzodiazepines and dementia by the use of other psychotropics (*i.e.* antidepressants, antipsychotics, mood stabilizers etc.) was another matter of concern. Indeed, a significant proportion of benzodiazepine users also used other psychotropics known to act on the central nervous system; some of them have putative deleterious effects on cognition owing to their pharmacological properties (*e.g.* anticholinergic effect). These comedications could explain, as least in part, the association found between benzodiazepines and dementia. We present below a preliminary work to assess whether the association found in BENZODEM (main cohort analysis, Part III) and BENZODEM2 (case-control study, Part IV) persisted after the influence of other psychotropics was neutralised.

3.1.2. Method

3.1.2.1. Analyses conducted within the PAQUID cohort

We used the source population and comparison groups described for the main prospective study (Part III). If an interaction was found not to be significant, a complementary adjustment was made (sensitivity analysis) on other psychotropics in order to assess the likelihood of confounding. We considered two definitions of other psychotropic use: (i) current use at index date, as considered (used?) for the main prospective BENZODEM/PAQUID study (*i.e.* five years after inclusion in the programme, T_5), the reference being non-users of other psychotropics at T_5, and (ii) current or past use at T_5, the reference being non-users of other psychotropics at T_5 and before this date. As sample size for each category was too small, we were not able to assess the potential modifying effect of the various types of other psychotropics or to consider them in the adjustment model (Table 34).

3.1.2.2. Analyses conducted within the RAMQ cohort

The RAMQ case-control study (Part IV) provided a sufficient sample size to assess the potential modifying or confounding effect of antidepressants. We chose to focus on antidepressants since: (i) they are often co-prescribed with benzodiazepines, (ii) they are the most frequently prescribed psychotropics after benzodiazepines, (iii) they are a marker of depression (cf. Part III, section 3.2.1.5) being considered as both a potential prodrome and a risk factor of dementia, and (iv) the sample sizes were too small for other categories of psychotropics. As in the PAQUID study, we first assessed the interaction between benzodiazepine and antidepressant uses. If not statistically significant, the putative confounding effect of antidepressants would be assessed by means of a complementary adjustment. We measured ever use of antidepressants during the same observation period as that considered for benzodiazepines (*i.e.* 5 years or more before the date of the first diagnosis of Alzheimer's disease reported in the database).

3.1.3. Results

3.1.3.1. PAQUID cohort

Among individuals included in the BENZODEM prospective programme (n=1063), 68 (6.4%) were current users of other psychotropics at the study start (14.7% among benzodiazepine new users *versus* 5.6% among non-users) and 119 (11.2%) were current or past-users at the study

start (31.6% among benzodiazepine new users *versus* 9.2% among non-users) (Table 34). Use of other psychotropics, whatever the definition considered, did not significantly modify the strength of the association between benzodiazepine initiation and Alzheimer's disease (P=0.84 for current use and P=0.88 for past or current use). Similarly, adjustment on other psychotropics considered as putative confounders did not alter the results (Odds Ratio, OR 1.58, 95%CI 1.05 to 2.38 for supplementary adjustment on current use of psychotropics and 1.54 (1.02 to 2.33) for supplementary adjustment on current or past use of psychotropics) (Table 35).

However, an independent but non-significant increased risk of dementia of about 40% was observed in users of other psychotropics, whatever the definition considered (Table 35). Although it was impossible, due to insufficient sample sizes (Table 34), to evaluate the effect of each category (*i.e.* antidepressants, antipsychotics, mood stabilizers and others), this excess risk associated with the use of non-benzodiazepine psychotropics raised again the problem of confounding by depression, anxiety or sleep disorders.

Table 34. Benzodiazepine and other psychotropic use at the BENZODEM study start (T_5)

Other psychotropics use at T_5 (*i.e.* non-benzodiazepines)	Benzodiazepine new users at T_5, n=95 (%)	Benzodiazepine non-users at T_5 and before, n=968 (%)	Total n=1063 (%)
All psychotropics:			
Current users	14 (14.7)	54 (5.6)	68
Past users	16 (16.8)	35 (3.6)	51
Non-users (at T_5 and before)	65 (68.4)	879 (90.8)	944
Antidepressants:			
Current users	9 (9.5)	21 (2.2)	30
Past users	5 (5.2)	11 (1.1)	16
Non-users (at T_5 and before)	81 (85.3)	936 (96.7)	1017
Antipsychotics:			
Current users	2 (2.1)	9 (0.9)	11
Past users	4 (4.2)	9 (0.9)	13
Non-users (at T_5 and before)	89 (93.7)	950 (98.1)	1039
Thymoregulators:			
Current users	0 (0.0)	0 (0.0)	0
Past users	1 (1.1)	0 (0.0)	1
Non-users (at T_5 and before)	94 (98.9)	968 (100.0)	1062
Other psychotropics:			
Current users	3 (3.2)	26 (2.7)	29
Past users	8 (8.4)	18 (1.8)	26
Non-users (at T_5 and before)	84 (88.4)	924 (95.5)	1008

Table 35. Complementary adjustment on other psychotropic use in the main cohort study of BENZODEM (Part III)

Benzodiazepine use at study start	Hazard ratio (95%CI) age, gender adjusted, n=1063	Multivariable hazard ratio (95%CI), n=983		
		Model 1*	Model 2†	Model 3‡
Non-users	1.00 (reference) n=968, cases=223	1.00 (reference) n=898, cases=203	1.00 (reference) n=898, cases=203	1.00 (reference) n=898, cases=203
New users	1.58 (1.08 to 2.31) n=95, cases=30	1.62 (1.08 to 2.43) n=85, cases=28	1.58 (1.05 to 2.38) n=85, cases=28 *Note/ HR§ for current use of other psychotropics: 1.39 (0.84-2.31) n=61, cases=17*	1.54 (1.02 to 2.33) n=85, cases=28 *Note/ HR§ for current or past use of other psychotropics: 1.40 (0.94-2.08) n=106, cases=30*

*Model 1: adjusted for age, gender, schooling duration, singleness, wine consumption, smoking, use of antihypertensive drugs, use of antidiabetic agents, use of statins, use of platelet inhibitors or oral anticoagulants at the study start (T_5), depressive symptoms and Mini-Mental State Examination evolution between inclusion (T_0) and three year follow-up visit (T_3).
†Model 2: Model 1 further adjusted for current use of psychotropics at T_5.
‡Model 3: Model 1 further adjusted for current or past use of psychotropics at T_5.
§Hazard Ratio.

3.1.3.2. RAMQ cohort

Among individuals included in the RAMQ case-control study (n=8980), 1610 (17.9%, 24.3% of cases and 16.3% of controls) were registered with at least one reimbursement for antidepressants during the study observation period (*i.e.* from 5 to 10 years) before the diagnosis of Alzheimer's disease, index date). Ever use of antidepressants during the observation period did not significantly alter the association found between benzodiazepine ever use and Alzheimer's disease (the interaction between benzodiazepine and antidepressant use was not significant P=0.74). This association remained significant after further adjustments on antidepressant use (Odds Ratio, OR 1.35, 95%CI 1.20 to 1.51). Moreover, as in the PAQUID study, we found an independent effect of antidepressants on the risk of dementia (OR 1.41 (1.23 to 1.62)) (Table 36).

Table 36. Complementary adjustment on antidepressant use in the case-control study using the RAMQ database (BENZODEM2, Part IV)

Benzodiazepine use 5 to 10 years before dementia	Cases n=1796 (%)	Controls n=7184 (%)	Univariable odds Ratio (95%CI)*	Multivariable odds ratio (95%CI)	
				Model 1*†	Model 2*†‡
Non-users	902 (50.2)	4311 (60.0)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Users	894 (49.8)	2873 (40.0)	1.52 (1.37-1.69)	1.43 (1.28-1.60)	1.35 (1.20-1.51) *Note/ OR§ for antidepressant use: (n=1610, cases=437) 1.41 (1.23-1.62)*

*Matched for age, gender and follow-up duration.
†Model 1: adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis), anxiety, depression and insomnia diagnoses assessed 5 to up to 10 years before Alzheimer's disease diagnosis.
‡Model 2: Model 1 further adjusted for antidepressant reimbursement assessed 5 to 10 years before Alzheimer's disease diagnosis.
§Odds Ratio.

3.1.4. Conclusion about the role of other psychotropics

The association between benzodiazepines and dementia remained, independently of other psychotropics (no interaction was found between benzodiazepine use and use of other psychotropics or antidepressants). The strength of association was roughly the same in PAQUID after complementary adjustment on other psychotropics. However, in the RAMQ study, the association was lower after adjusting on antidepressants. Because the independent effect of psychotropics was about 40% and was significant for antidepressants, this opened up the debate about the intrinsic effect of other psychotropics on dementia, possibly synergistic with benzodiazepines and more generally about the role of protopathic bias on this association.

3.2. Is there an independent effect of other psychotropics or a synergistic effect with benzodiazepines on the risk of dementia?

3.2.1. Objective

The above conclusions led to subsequent analyses in order to evaluate: (i) the potential synergistic relationship between benzodiazepines and other psychotropics compared to benzodiazepines alone regarding the risk of dementia, (ii) the potential independent relationship between the use of other psychotropics compared to non-use of any psychotropics regarding this risk.

3.2.2. Method

3.2.2.1. PAQUID cohort

Using the same sample as for the case-control study conducted in the BENZODEM programme (Part III), we first considered several categories regarding ever use of benzodiazepines or other psychotropics before index date: (i) exposed to benzodiazepines but not to other psychotropics, (ii) exposed to benzodiazepines and to other psychotropics, (iii) exposed to psychotropics but not to benzodiazepines, (iv) never exposed to benzodiazepines or to other psychotropics (reference group). One additional category included individuals with missing data, which created uncertainty about their exposure status.
Next, we considered benzodiazepine and other psychotropic use by time period preceding index date (*recent initiation i.e.* less than 5 years before index date and *past initiation i.e.* 5 years or

more before this date) to evaluate the influence of a putative protopathic bias (expected to occur mostly for exposures initiated in the few years preceding dementia diagnosis). This led us to consider eight new categories of exposure (cf. Table 38), the reference category remaining unchanged (*i.e.* never exposed to benzodiazepines or to other psychotropics). One additional category grouped individuals with missing data, which created uncertainty about their exposure status.

We estimated the relationship between exposure to benzodiazepines and to other psychotropics according to the two approaches described above (*i.e.* ever use whatever the period and ever use considering recent or past initiation). Analyses were adjusted on the confounders listed in Part III for the main case-control analysis of the BENZODEM programme.

3.2.2.2. RAMQ cohort

We used the cases and controls groups from the RAMQ study (BENZODEM2, Part IV) to assess the putative synergic effect of antidepressants and benzodiazepines (antidepressants being most often prescribed with benzodiazepines). Benzodiazepine and antidepressant exposure were observed during the 5 to 10 years preceding Alzheimer's disease diagnosis. We considered (i) users of benzodiazepines but not of antidepressants, (ii) users of benzodiazepines and antidepressants, (iii) users of antidepressants only, and (iv) never users of benzodiazepines or antidepressants (reference group). Matched cases and controls were compared regarding these four categories of exposure. Models were adjusted on the confounders listed in Part IV (BENZODEM2 study).

3.2.3. Results

3.2.3.1. PAQUID cohort

Considering the whole period preceding the dementia diagnosis, 96 cases (20.6%) and 260 controls (14.4%) had used both benzodiazepines and other psychotropics. Of the 444 users of other psychotropics, 356 (80.2%) had also used benzodiazepines (same proportion for cases and controls). Of the 892 benzodiazepine users, 39.9% had also used other psychotropics (45.7% of cases and 38.1% of controls). Using both benzodiazepines and other psychotropics was associated with a significant 80% increased risk of dementia, compared to never use of psychotropics recorded before the diagnosis of dementia. This risk was higher than for users of benzodiazepines or other psychotropics alone (Table 37).

Table 37. Association between benzodiazepine and other psychotropic ever use in the case-control study using the PAQUID database (BENZODEM, Part III)

Benzodiazepine and other psychotropic ever use before dementia	Cases n=467 (%)	Controls n=1810 (%)	Univariable odds ratio (95% CI)*	Multivariable odds ratio (95%CI)	
				Model 1*†	Model 2*‡
Non-users	134 (28.7)	661 (36.5)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Benzodiazepine users	114 (24.4)	422 (23.3)	1.35 (1.02 to 1.78)	1.33 (1.00 to 1.76)	1.32 (0.99 to 1.75)
Benzodiazepine and other psychotropic users	**96 (20.6)**	**260 (14.4)**	**1.90 (1.40 to 2.59)**	**1.79 (1.30 to 2.45)**	**1.80 (1.30 to 2.48)**
Other psychotropic users	23 (4.9)	65 (3.6)	1.75 (1.04 to 2.94)	1.66 (0.98 to 2.82)	1.63 (0.96 to 2.76)
Missing exposures	100 (21.4)	402 (22.2)	1.26 (0.94 to 1.69)	1.08 (0.79 to 1.48)	1.01 (0.74 to 1.39)

*Matched for age and gender.
†Model 1: adjusted for schooling duration, singleness, wine consumption, use of antihypertensive drugs, use of antidiabetic agents, use of statins, use of platelet inhibitors or oral anticoagulants, 7 or 8 years before index date.
‡Model 2: Model 1 further adjusted for significant depressive symptoms according to Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women).

Considering the date of drug initiation for individuals who had declared both benzodiazepine and other psychotropic use before the dementia diagnosis, a statistically significant increased risk was found for past initiators of both benzodiazepines and other psychotropics (adjusted OR 1.91, 95%CI 1.34 to 2.71). A higher but non-significant association (2.50-fold increased risk) was found in the group of recent initiators of both benzodiazepines and other psychotropics. This raised concern about a possible protopathic bias but as the sample size was rather small, a random effect was not excluded which precluded any clear-cut conclusion. No association was found in the group of recent initiators of benzodiazepines and past initiators of other psychotropics. Finally, past initiation of benzodiazepines and recent initiation of other psychotropics led to a non-significant 60% excess risk due to low sample size, but this was very similar to the main cohort approach when adjustment was made considering other psychotropics. (Table 38).

A non-significant 60% increased risk of dementia was found for ever use of other psychotropics only (Table 37). This risk seemed mostly explained by the recent use (non-significant 85% increased risk for recent initiators *versus* 56% increased risk in past initiators) (Table 38).

Interestingly, past users of benzodiazepines with no other psychotropic during the entire period preceding dementia had a 30% increased risk of dementia, bordering statistical significance (Table 38).

Table 38. Association between benzodiazepine and other psychotropic use (considering period of use, *i.e.* recent or past initiation) in the case-control study nested in PAQUID programme (BENZODEM, Part III)

Benzodiazepine and other psychotropic ever use before dementia	Cases n=467 (%)	Controls n=1810 (%)	Univariable odds ratio (95% CI)*	Multivariable odds ratio (95%CI)	
				Model 1*†	Model 2*‡
Never users of benzodiazepines or other psychotropics	134 (28.7)	661 (36.5)	1.00 (reference)	1.00 (reference)	1.00 (reference
Benzodiazepine recent initiators	9 (1.9)	30 (1.7)	1.46 (0.69 to 3.13)	1.46 (0.68 to 3.15)	1.44 (0.67 to 3.10)
Benzodiazepine past initiators	**105 (22.5)**	**392 (21.6)**	**1.34 (1.00 to 1.79)**	**1.32 (0.99 to 1.77)**	**1.31 (0.98 to 1.76)**
Benzodiazepine and other psychotropic recent initiators	2 (0.4)	3 (0.2)	3.40 (0.56 to 20.51)	2.52 (0.41 to 15.39)	2.50 (0.41 to 15.2)
Benzodiazepine recent and other psychotropic past initiators	4 (0.9)	17 (0.9)	1.25 (0.41 to 3.83)	1.02 (0.33 to 3.16)	0.99 (0.32 to 3.08)
Benzodiazepine past and other psychotropic recent initiators	14 (3.0)	43 (2.4)	1.65 (0.88 to 3.09)	1.57 (0.83 to 2.98)	1.62 (0.85 to 3.08)
Benzodiazepine and other psychotropic past initiators	**76 (16.3)**	**197 (10.9)**	**1.98 (1.41 to 2.77)**	**1.89 (1.34 to 2.67)**	**1.91 (1.34 to 2.71)**
Other psychotropic recent initiators	6 (1.3)	12 (0.7)	2.14 (0.74 to 6.16)	1.88 (0.65 to 5.50)	1.85 (0.64 to 5.41)
Other psychotropic past initiators	17 (3.6)	53 (2.9)	1.66 (0.93 to 2.96)	1.60 (0.89 to 2.89)	1.56 (0.87 to 2.83)
Missing exposures	100 (21.4)	402 (22.2)	1.26 (0.93 to 1.69)	1.08 (0.79 to 1.47)	1.01 (0.74 to 1.39)

*Matched for age and gender.
†Model 1: adjusted for schooling duration, singleness, wine consumption, use of antihypertensive drugs, use of antidiabetic agents, use of statins, use of platelet inhibitors or oral anticoagulants, 7 or 8 years before index date.
‡Model 2: Model 1 further adjusted for significant depressive symptoms according to Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women).

3.2.3.2. RAMQ cohort

Of the 8980 individuals included in the RAMQ study, 1157 (12.9%) used both benzodiazepines and antidepressants (18.4% of cases and 11.5% of controls). As previously mentioned, most antidepressant users (71.9%, n=1610) had also used benzodiazepines during the study period (75.7% of cases and 70.4% of controls). The contrary was found for benzodiazepine users (n=3767), for whom antidepressant use was less common (30.7%, 37.0% of cases and 28.8% of controls) (Table 39). A significant independent effect was found for benzodiazepine and antidepressant users compared to non-users of these drugs (risk increased by about 40% and 50%, respectively). The estimate was higher for users of both benzodiazepines and antidepressants during the study period (Odds Ratio 2.04, 95%CI 1.61 to 2.23) (Table 39).

Table 39. Association between benzodiazepine and antidepressant ever use (observed 5 to 10 years before Alzheimer's disease diagnosis) in the RAMQ case-control study (BENZODEM2, Part IV)

Benzodiazepine or antidepressant use *(5 to 10 years before dementia)*	Cases n=1796 (%)	Controls n=7184 (%)	Univariable odds ratio (95% CI)*	Multivariable odds ratio (95%CI)	
				Model 1*†	Model 2*‡
Non-users	796 (44.3)	3964 (55.2)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Benzodiazepine users *(non-use of benzodiazepines during the study period)*	563 (31.4)	2047 (28.5)	1.40 (1.24 to 1.58)	1.40 (1.23 to 1.58)	1.36 (1.20 to 1.55)
Benzodiazepine and antidepressant users	331 (18.4)	826 (11.5)	2.04 (1.76 to 2.38)	2.03 (1.74 to 2.37)	2.04 (1.61 to 2.23)
Antidepressant users *(non-use of benzodiazepines during the study period)*	106 (5.9)	347 (4.8)	1.52 (1.21 to 1.92)	1.51 (1.20 to 1.91)	1.52 (1.15 to 1.85)

*Matched for age, gender and follow-up duration.
†Model 1: adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis), assessed 5 to 10 years before Alzheimer's disease diagnosis.
‡Model 2: Model 1 further adjusted for antidepressant reimbursement assessed 5 to 10 years before Alzheimer's disease diagnosis.

3.2.4. Conclusion about the independent or synergistic effect of other psychotropics

The strength of the association between benzodiazepines and dementia increased when other psychotropics (PAQUID) or antidepressants (RAMQ) initiated long before dementia were associated. A non-significant association was found between other psychotropics and dementia, mostly due to recent users (PAQUID). A significant independent association was found for past initiators of antidepressants (RAMQ).

3.3. Discussion about other psychotropic use and dementia

3.3.1. Validity of the relation between benzodiazepine use and dementia considering other psychotropic use

The association between benzodiazepines and dementia persisted in the absence of use of other psychotropics (PAQUID) or antidepressants (RAMQ) (benzodiazepines-other psychotropics interaction was non-significant, benzodiazepines-dementia relationship was non-modified by adjustment on other psychotropics or antidepressants). Since other psychotropics are often co-prescribed with benzodiazepines, a certain degree of colinearity could have jeopardized the validity of the estimates when the adjustment model considered the 2 exposures. This is the reason why this analysis was not presented in the manuscript submitted for publication. In a subsequent analysis (initially conducted to assess the synergistic action of benzodiazepines and other psychotropics on the risk of dementia or an independent action of the latter), we created a variable categorised according to (i) benzodiazepine and other psychotropic (PAQUID) or

antidepressant (RAMQ) use, and (ii) the period of use (as there is a risk of protopathic bias for recent initiations). Using the PAQUID data, benzodiazepine past-initiation (without other psychotropics) compared to never-users of psychotropics (*i.e.* benzodiazepines and others) was associated with a 30% increase in the risk of dementia, approaching statistical significance. This estimate was similar to that found using the RAMQ database when benzodiazepine past initiation (without other psychotropics) was compared to never-use of benzodiazepines and antidepressants. These last findings reinforced the argument for an independent effect of benzodiazepines whatever the use of other psychotropics.

3.3.2. Association between other psychotropics and dementia independently of benzodiazepines

Using the PAQUID cohort, other psychotropic use was found to be associated with a 60% increased risk of dementia compared to non-use of both other psychotropics and benzodiazepines. This result seemed mostly explained by the recent use of other psychotropics, raising a concern about a potential putative protopathic bias. However, this result should be interpreted with caution since the low sample sizes precluded significance and did not allow evaluation of each category of psychotropics which have both distinct pharmacological properties and putative effects on cognitive functions.
Using the RAMQ database, a 40% increased risk of Alzheimer's disease, independent of benzodiazepine use, was found for antidepressant use initiated more than 5 years before the disease. The meaning of this result was unclear: (i) it could express a deleterious effect on the part of antidepressants (*e.g.* by means of anticholinergic properties), (ii) antidepressants could be the marker of a condition, *i.e.* depression, being associated with a higher risk of dementia.

3.3.3. Synergistic effects of benzodiazepines and other psychotropics on the risk of dementia

Compared to non-use of psychotropics, exposure to both benzodiazepines and other psychotropics (PAQUID) or antidepressants (RAMQ) during a period preceding dementia by more than 5 years resulted in a higher risk of dementia than when benzodiazepines were used alone. Interpretation of these results is complex. On the one hand, other psychotropics could add their deleterious effects on cognitive functions to those of benzodiazepines. On the other hand, using both benzodiazepines and other psychotropics (mainly antidepressants) may correspond to more severe forms of psycho-affective disorders which are suspected to be a risk factor for dementia. Combined use would be a marker of patients with a higher risk of dementia.

This last hypothesis could not be tested in the PAQUID cohort since doses and real durations of treatments were not assessed by the programme.

3.4. Conclusion about other psychotropic use and dementia

Our conclusions were not modified when considering other psychotropics. The issue of an independent or synergistic effect of other psychotropics was addressed when we completed our complementary analyses. However, answering these questions was outside the scope of our research (*i.e.* evaluation of the relation between benzodiazepines and dementia) and would require at least a specific protocol if we were attempting to draw valid conclusions. This would require access to a population database of quite a large sample size to work with sufficient statistical power on each category of psychotropics. Reasonable assumptions regarding the biological mechanism for their putative effects on cognition should be considered as a starting point for designing these new protocols.

4. Pathogenesis of the relationship

4.1. Context and objective

Although several studies, including ours, have associated benzodiazepine use to an increased risk of dementia in the elderly (Parts II, III, IV), the mechanism underlying this association, which would have a major public health impact if causal (Part I), remained unknown. The long-term effect of benzodiazepine use on cognition is debated.[137] Some studies showed an accelerated cognitive decline in users[184-191] while others did not.[124 176 177] These discrepant findings may result from differences in the definitions of benzodiazepine exposure, cognitive outcome, or follow-up duration.[137] Moreover, none of these studies considered the putative association between benzodiazepine use and dementia in their analyses, even though a cognitive decline related to dementia could jeopardize the estimation of the intrinsic role of benzodiazepines on cognition. We therefore conducted a cohort study within the PAQUID programme to evaluate the effect of new benzodiazepine use on long-term cognitive decline in initially dementia-free elderly participants, considering the concomitant risk of dementia.

4.2. Hypothesis

Independently of the acute effects of benzodiazepines on cognitive functions, a worsening of cognitive decline starting shortly after initiation of the treatment would indicate a protopathic

association. Indeed, in these cases there is a good chance that prescriptions of benzodiazepines have been initiated to treat a prodrome of the disease. Conversely, this would not be the case for declines occurring long after starting the treatment, *e.g.* 5 years or more. A causal mechanism could be evoked if a higher proportion of cognitive decline appeared in individuals who had started benzodiazepines and if the risk was delayed in time.

4.3. Method

4.3.1. Design, setting

A cohort study was conducted among elderly participants included in the prospective PAQUID programme (described in Part III). Non-users of benzodiazepines at baseline and without dementia at the third year of follow-up (T_3, index date) were eligible.

4.3.2. Exposure

For the present study, all eligible subjects were classified as benzodiazepine new users or non-users according to exposure ascertainment at T_3. Subjects with no declaration of benzodiazepine use at T_0 and T_3 were classified as non-users; subjects with no declaration of benzodiazepine use at T_0 and declaration of benzodiazepine use at T_3 were classified as new users. Subsequent exposure to benzodiazepines was not taken into account in the main analyses.

4.3.3. Outcome

New users of benzodiazepines at index date were compared to non-users at this date regarding changes in cognitive performances measured over the follow-up since T_3, according to (i) the Mini-Mental State Examination (MMSE) measuring global cognitive functioning,[152] (ii) the Isaacs Set Test (IST) measuring[154] verbal fluency and memory, and (iii) the Benton Visual Retention Test (BVRT) measuring visual perception, memory and constructional abilities.[153] For all selected subjects, temporal trends of their cognitive functions were investigated at follow-up visits conducted every 2-3 years after T_3. The MMSE, although being the most widely used test, has limited sensitivity for identifying changes in the highest levels of cognition; conversely, the sensitivity of IST is maintained across the whole range of the cognition scale. Possible scores range from 0 to 30 for the MMSE, from 0 to 40 for the IST, and from 0 to 15 for the BVRT. For these three tests, the lower the score, the worse the global cognitive functioning. Participants were censored at the date of follow-up of their last available score. For each cognitive test and

participant, missing values before the last available score were imputed by using the trend of the score evaluated from the closest available data.

4.3.4. Statistical analysis

The association between incident exposure to benzodiazepines and the trend of cognitive performances was studied using non-linear mixed models, considering a latent process as dependent variable. These models were chosen to correct for the metrological properties of the cognitive tests used, especially their non-constant sensitivity to a given change (curvilinearity). It has recently been shown to provide correct estimates of the associations between potential risk factors and cognitive evolution when measured by the MMSE.[192] [193] Crude models were adjusted for age at inclusion and age in interaction with time after inclusion. Multivariate models were adjusted for constant variables (age, gender, educational level measured at index date (T_3)), and time-dependent ones (wine consumption, celibacy, use of other psychotropics, depression and use of cardiovascular drugs: antihypertensive drugs, antidiabetic agents, statins, oral anticoagulants, and platelet inhibitors) were measured repeatedly all throughout follow-up. Sensitivity analyses were performed: (i) cognitive data were censored at the follow-up time before a subject was diagnosed with dementia in order to exclude cognitive declines related to the prodromal phase of dementia; (ii) for each participant, cognitive data were censored at the time the exposure to benzodiazepine changed, *i.e.* at the time new users became non-users or non-users reported benzodiazepine use in order to take into account the dynamics of exposure; (iii) study population was restricted to participants without a diagnosis of dementia during follow-up in order to eliminate the potential effect of dementia on cognitive decline.

4.4. Results

Of the 3777 subjects included in the PAQUID programme, 1303 were eligible. Among benzodiazepine non-users at inclusion, 167 benzodiazepine new users and 1136 non-users, all free of dementia, were identified at index date. Compared to non-users, benzodiazepine new users were more likely to be women (63.5% *versus* 50.3%), to have a lower wine consumption (48.5% *versus* 60.8%), to be single (47.3% *versus* 39.5%), and to present depressive disorders (14.6% *versus* 5.1%) (Table 40). Cognition level appeared similar at index date between benzodiazepine new users and non-users. No longitudinal effect of benzodiazepine new use was found, whatever the cognitive test used (MMSE, P=0.19; IST, P=0.08; BRVT, P=0.85).

Table 40. Baseline characteristics of benzodiazepine new users and non-users

	New users (n=167)	Non-users (n=1136)	P value
Female gender (n, %)	106 (63.5)	572 (50.3)	0.01
Age (years), mean (s-d.)	77.5 (5.7)	76.5 (6.1)	0.24
Education level ≥7 years (n, %)	123 (73.6)	848 (74.6)	0.78
Wine consumption (n, %)	81 (48.5)	691 (60.8)	0.01
Married (n, %)	88 (52.7)	687 (60.5)	0.01
Antihypertensive drug use (n, %)	92 (55.1)	628 (55.3)	0.90
Statin use (n, %)	5 (3.0)	35 (3.1)	0.95
Oral anticoagulants or platelet inhibitor use (n, %)	10 (5.9)	49 (4.3)	0.32
Antidiabetic agent use (n, %)	10 (6.0)	86 (7.6)	0.53
Depression			
CES-D* score (mean, sd.)	10.8 (9.7)	5.5 (6.6)	$<10^{-3}$
Depressive symptoms (n, %)	23 (14.6)	56 (5.1)	$<10^{-3}$
Cognitive scores (mean, sd.)			
MMSE†	26.6 (2.7)	27.1 (2.6)	0.17
IST‡	27.9 (5.6)	29.5 (5.7)	0.76
BVRT§	10.9 (2.4)	11.4 (2.3)	0.62

*CES-D: Center for Epidemiologic Studies Depression scale.
†MMSE: Mini-Mental State Examination.
‡IST: Isaacs Set Test.
§BVRT: Benton Visual Retention Test.

Table 41. Effect of benzodiazepine new use on cognitive level and decline according to Mini-Mental State Examination, Isaacs Set Test, and Benton Visual Retention test

Mini-Mental State Examination	**Crude model (n=1303)**			**Adjusted model* (n=1266)**		
Variable	***Estimate†***	***SE‡***	***P value***	***Estimate†***	***SE‡***	***P value***
Time	0.07	0.02	$<10^{-3}$	0.08	0.03	0.09
Age at inclusion	-0.83	0.07	$<10^{-3}$	-0.60	0.08	$<10^{-3}$
Age at inclusion x time	-0.12	0.01	$<10^{-3}$	-0.09	0.01	$<10^{-3}$
Cross-sectional effect for benzodiazepines	-0.27	0.13	0.03	-0.17	0.14	0.20
Longitudinal effect for benzodiazepines x time	0.01	0.02	0.60	0.03	0.03	0.19
Isaacs Set Test	**Crude model (n=1189)**			**Adjusted model* (n=1170)**		
	Estimate†	***SE‡***	***P value***	***Estimate†***	***SE‡***	***P value***
Time	-0.08	0.02	$<10^{-3}$	-0.10	0.03	0.01
Age at inclusion	-0.82	0.08	$<10^{-3}$	-0.73	0.09	$<10^{-3}$
Age at inclusion x time	-0.10	0.01	$<10^{-3}$	-0.09	0.01	$<10^{-3}$
Cross-sectional effect for benzodiazepines	-0.31	0.14	0.03	-0.35	0.16	0.03
Longitudinal effect for benzodiazepines x time	0.02	0.02	0.14	0.04	0.02	0.08
Benton Visual Retention test	**Crude model (n=1117)**			**Adjusted model* (n=1101)**		
	Estimate†	***SE‡***	***P value***	***Estimate†***	***SE‡***	***P value***
Time	-0.02	0.01	0.22	0.02	0.03	0.47
Age at inclusion	-0.79	0.07	$<10^{-3}$	-0.59	0.08	$<10^{-3}$
Age at inclusion x time	-0.05	0.01	$<10^{-3}$	-0.06	0.01	$<10^{-3}$
Cross-sectional effect for benzodiazepines	-0.30	0.12	0.01	-0.25	0.14	0.07
Longitudinal effect for benzodiazepines x time	0.01	0.01	0.73	0.01	0.02	0.85

*Adjusted for: gender, education level, wine consumption, married, depression, dementia, psychotropic use, cardiovascular drug use.
†Using non-linear mixed model considering a latent process as dependent variable.
‡SE: standard error of the estimate.

4.5. Discussion about the pathogenesis of the relationship

Benzodiazepine initiation was not associated with a difference in the temporal trend of cognitive performances. This cohort study considering the concomitant risk of dementia did not objective any specific effect of benzodiazepine initiation on cognitive level or on cognitive decline in the elderly.

These results might at first appear contradictory, given the association found between benzodiazepines and dementia, but they are not. First, any alteration in cognitive functioning is not always a marker for dementia. Second, these results ruled out several criticisms levelled against the validity of the relation found between benzodiazepines and dementia, such as protopathic bias.

After this new complementary study, we were able to state that the link between benzodiazepines and dementia was real, at least from a statistical point of view. The mechanism explaining this association remained unresolved, although several hypotheses will be put forward in Part VI. The abstract of a manuscript related to this study and currently in the submission process (Benzodiazepines new use and long-term cognitive decline in elderly: a prospective cohort study) can be found in Annexes 1.

5. Characteristics associated with psychotropic use

5.1. Characteristics associated with psychotropic consumption in rural areas: a cross-sectional study using a cohort of retired farmers (AMI)

5.1.1. Context and objective

Living in a rural area could account for some specificities (*e.g.* lower density of doctors, isolation, lower educational level, lower income, more physical activities, healthier diet, stronger familial support, etc.) leading to possible differences with regard to determinants of psychotropic use compared with the general population. Our aim was to evaluate the prevalence and characteristics of psychotropic use (in general and for the main families: benzodiazepines and antidepressants) in individuals living in a rural area of which little was known.

5.1.2. Population, Method

We conducted a cross-sectional study in AMI, a population-based cohort set up to study the ageing of a rural population. Between 2007 and 2009, 1002 subject aged 65 years and over, living in rural areas in Gironde and retired from agricultural work after at least 20 years of activity, were randomly sampled from individuals registered in the agricultural Health Insurance programme (Mutualité Sociale Agricole, MSA). Visits were planned every 2 years with telephone interviews in between. Information was collected about living habits, health conditions including drug consumption, cognition, and dependency. A clinical assessment was made of all subjects suspected of presenting a dementia and confirmed by a senior neurologist. Data on the reimbursement of drugs, medical and paramedical care by the MSA programme were available. Characteristics of the AMI cohort have been previously described.[194]

5.1.3. Main conclusions

The AMI data at inclusion showed a lower prevalence of psychotropic use compared with what had been shown in the general population as, for example, by the PAQUID programme. This difference was less pronounced for men than women but persisted whatever the sex for benzodiazepines (Table 42). Results from a multivariate logistic regression highlighted the characteristics associated with use already identified in the general population such as: female gender, higher age (for benzodiazepines), lower age (for antidepressants), lower life-satisfaction, polypathologies, living in an institution, consumption of other psychotropics for benzodiazepine and antidepressant use. However, some specificities appeared: depressive disorders were more often associated with antidepressant than benzodiazepine use, anxiety was associated with antidepressant but not with benzodiazepine use, a higher level of dependency was associated with a higher psychotropic consumption (mainly antidepressants) but with a lower consumption of benzodiazepines (Table 43). Finally, cognitive disorders without dementia (MCI) were associated with a higher consumption of antidepressants but not of benzodiazepines (Table 43). The abstract of a manuscript related to this study and in preparation for submission (Characteristics associated with psychotropic use in a French cohort of elderly farmers) can be found in Annexes 1.

Table 42. Comparison between psychotropic users and non-users in the AMI cohort at inclusion

	Psychotropic use			Benzodiazepine use			Antidepressant use		
	Yes n=284 (%)	No n=704 (%)	P value	Yes n=204 (%)	No n=783 (%)	P value	Yes n=98 (%)	No n=889 (%)	P value
Female gender	141 (49.7)	231 (32.8)	$<10^{-3}$	107 (52.5)	265 (33.8)	$<10^{-3}$	55 (56.1)	317 (35.6)	$<10^{-3}$
Age (years):			$<10^{-3}$			$<10^{-3}$			0.02
65-74	94 (33.1)	365 (51.9)		67 (32.8)	392 (50.1)		34 (34.7)	425 (47.8)	
75-84	149 (52.5)	281 (39.9)		108 (52.9)	322 (41.1)		49 (50.0)	381 (42.9)	
≥85	41 (14.4)	58 (8.2)		29 (14.2)	69 (8.8)		15 (15.3)	83 (9.3)	
Single or widowed	85 (29.9)	147 (20.9)	0.01	59 (28.9)	173 (22.1)	0.04	31 (31.6)	201 (22.6)	0.05
Having children	257 (90.5)	646 (91.8)	0.52	186 (91.2)	716 (91.4)	0.90	93 (94.9)	809 (91.0)	0.19
Income:			0.45			0.32			0.23
low	66 (23.4)	139 (19.8)		53 (26.1)	152 (19.5)		16 (16.5)	189 (21.3)	
medium	101 (35.8)	245 (34.9)		67 (33.0)	279 (35.8)		34 (35.1)	312 (35.2)	
high	63 (22.3)	180 (25.6)		49 (24.1)	194 (24.9)		22 (22.7)	221 (24.9)	
does not wish to respond	9 (3.2)	35 (5.0)		7 (3.5)	37 (4.7)		3 (3.1)	41 (4.6)	
does not know	43 (15.3)	103 (14.7)		27 (13.3)	118 (15.1)		22 (22.7)	123 (13.9)	
Living in institution	17 (6.0)	14 (2.0)	10^{-3}	12 (5.9)	19 (2.4)	0.01	8 (8.3)	23 (2.6)	0.01
Schooling duration (years):			10^{-3}			0.11			0.08
<7	167 (59.2)	357 (50.7)		121 (59.3)	402 (51.5)		53 (54.6)	470 (52.9)	
7	86 (30.5)	209 (29.7)		56 (27.4)	239 (30.6)		35 (36.1)	260 (29.3)	
>7	29 (10.3)	138 (19.6)		27 (13.2)	140 (17.9)		9 (9.3)	158 (17.8)	
Life satisfaction:			$<10^{-3}$			$<10^{-3}$			$<10^{-3}$
bad	87 (30.6)	112 (15.9)		69 (33.8)	130 (16.6)		35 (35.7)	164 (18.5)	
good	73 (25.7)	245 (34.8)		58 (28.4)	260 (33.2)		18 (18.4)	300 (33.8)	
very good	92 (32.4)	300 (42.6)		62 (30.4)	329 (42.0)		29 (29.6)	362 (40.7)	
Depressive symptoms*	27 (9.5)	20 (2.8)	$<10^{-3}$	21 (10.3)	26 (3.3)	$<10^{-3}$	16 (16.3)	31 (3.5)	$<10^{-3}$
Anxiety symptoms†:			$<10^{-3}$			0.01			$<10^{-3}$
no	110 (38.7)	383 (54.4)		84 (41.2)	408 (52.1)		22 (22.5)	470 (52.9)	
light	96 (33.8)	219 (31.1)		70 (34.3)	245 (31.3)		37 (37.8)	278 (31.3)	
moderate to severe	21 (7.4)	34 (4.8)		18 (8.8)	37 (4.7)		10 (10.2)	45 (5.1)	
Other psychotropic use	-	-		59 (28.9)	79 (10.1)	$<10^{-3}$	58 (59.2)	185 (20.8)	$<10^{-3}$
Number of non-psychotropic drugs used:			$<10^{-3}$			$<10^{-3}$			0.12
0-3	67 (23.7)	279 (39.6)		42 (20.6)	304 (38.8)		30 (30.6)	316 (35.6)	
4-6	90 (31.8)	248 (35.2)		67 (32.8)	271 (34.6)		29 (29.6)	309 (34.8)	
≥7	126 (44.5)	177 (25.1)		95 (46.6)	208 (26.6)		39 (39.8)	264 (29.7)	
Frequency of medical visits:			$<10^{-3}$			$<10^{-3}$			$<10^{-3}$
≥once a month	164 (59.0)	231 (33.1)		118 (58.4)	276 (35.7)		61 (64.9)	333 (37.8)	
every 2 months	68 (24.5)	162 (23.2)		49 (24.3)	181 (23.4)		19 (20.2)	211 (24.0)	
3-4 times a year	42 (15.1)	228 (32.7)		31 (15.4)	239 (30.9)		13 (13.8)	257 (29.2)	
less frequently	4 (1.44)	77 (11.0)		4 (2.0)	77 (10.0)		1 (1.1)	80 (9.1)	
Dependency‡:			$<10^{-3}$			$<10^{-3}$			$<10^{-3}$
no	41 (14.9)	275 (40.6)		33 (16.7)	283 (37.5)		14 (14.9)	302 (35.2)	
light	117 (42.4)	286 (42.2)		91 (46.0)	312 (41.3)		28 (29.8)	375 (43.7)	
moderate	76 (27.5)	91 (13.4)		54 (27.3)	113 (15.0)		29 (30.9)	138 (16.1)	
severe	42 (15.2)	26 (3.8)		20 (10.1)	47 (6.2)		23 (24.5)	44 (5.1)	
Cognitive level:			$<10^{-3}$			0.01			$<10^{-3}$
normal	196 (69.8)	616 (88.3)		154 (75.9)	657 (84.8)		57 (58.8)	754 (85.6)	
Mild Cognitive Impairment	22 (7.8)	26 (3.7)		12 (5.9)	36 (4.7)		11 (11.3)	37 (4.2)	
dementia	63 (22.4)	56 (8.0)		37 (18.2)	82 (10.6)		29 (29.9)	90 (10.2)	
Alcohol consumption:			$<10^{-3}$			0.01			0.01
no	98 (34.5)	148 (21.0)		66 (32.4)	179 (22.9)		38 (38.8)	207 (23.3)	
every day, >3 glasses	9 (3.2)	68 (9.7)		6 (2.9)	71 (9.1)		3 (3.1)	74 (8.3)	
every day, ≤3 glasses	107 (37.7)	308 (43.8)		83 (40.7)	332 (42.4)		32 (32.7)	383 (43.1)	
at least once a week	31 (10.9)	79 (11.2)		20 (9.8)	90 (11.5)		11 (11.2)	99 (11.1)	
less frequently	6 (2.1)	27 (3.8)		5 (2.5)	28 (3.6)		2 (2.0)	31 (3.5)	
Tobacco use:			0.34			0.41			0.04
never	172 (60.6)	396 (56.3)		124 (60.8)	444 (56.7)		65 (66.3)	503 (56.6)	
past use	75 (26.4)	214 (30.4)		51 (25.0)	237 (30.3)		18 (18.4)	270 (30.4)	
current use	7 (2.5)	28 (4.0)		6 (2.9)	29 (3.7)		2 (2.0)	33 (3.7)	

*According to Center for Epidemiologic Studies Depression scale[156] (score ≥17 for men; ≥23 for women).

†According to Spielberger state anxiety scale[195] (≤20 no symptoms; 21 to 35 light symptomatology; ≥36 moderate to severe symptomatology).

‡According to the Rosow-Breslau Functional health scale[196], the Lawton Instrumental Activity of Daily Living (IADL) scale[197] and the Katz Activity of Daily Living (ADL) scale[198] (light if at least one item of Rosow scale is altered, moderate if at least one item of Rosow and IADL scales are altered and severe if at least one item of Rosow, IADL and ADL scales are altered.

Table 43. Characteristics associated with psychotropic use in persons 65 years and older included in the AMI cohort

	Multivariable Odds Ratio (IC95%)		
	Psychotropic users (n=284) *versus* non-users (n=704)	**Benzodiazepine users (n=204) *versus* non-users (n=783)**	**Antidepressant users (n=98) *versus* non-users (n=889)**
Female gender	**1.75 (1.11 to 2.75)**	**2.55 (1.53 to 4.25)**	1.16 (0.56 to 2.40)
Age (years):			
65-74	1.00 (reference)	1.00 (reference)	1.00 (reference)
75-84	1.34 (0.90 to 1.98)	**1.81 (1.16 to 2.83)**	0.77 (0.40 to 1.48)
≥85	1.09 (0.56 to 2.09)	**2.13 (1.05 to 4.33)**	**0.31 (0.10 to 0.92)**
Single or widowed	1.12 (0.74 to 1.69)	0.86 (0.54 to 1.35)	1.63 (0.85 to 3.14)
Having children	0.91 (0.50 to 1.65)	1.00 (0.52 to 1.92)	2.81 (0.85 to 9.35)
Income:			
low	1.00 (reference)	1.00 (reference)	1.00 (reference)
medium	0.95 (0.61 to 1.49)	0.63 (0.38 to 1.03)	1.34 (0.62 to 2.88)
high	1.13 (0.67 to 1.91)	0.96 (0.55 to 1.70)	1.51 (0.63 to 3.64)
does not wish to respond	**0.41 (0.16 to 1.05)**	0.45 (0.16 to 1.26)	0.51 (0.09 to 2.99)
does not know	**0.49 (0.26 to 0.93)**	**0.43 (0.21 to 0.86)**	1.53 (0.59 to 3.96)
Living in institution	1.60 (0.46 to 5.58)	**3.99 (1.00 to 15.99)**	1.01 (0.17 to 5.89)
Schooling duration (years):			
<7	1.00 (reference)	1.00 (reference)	1.00 (reference)
7	1.01 (0.68 to 1.50)	0.85 (0.54 to 1.33)	1.80 (0.95 to 3.38)
>7	0.69 (0.39 to 1.24)	1.05 (0.56 to 1.96)	0.91 (0.34 to 2.46)
Life satisfaction:			
bad	1.00 (reference)	1.00 (reference)	1.00 (reference)
good	**0.48 (0.30 to 0.76)**	**0.52 (0.31 to 0.86)**	0.60 (0.28 to 1.31)
very good	**0.65 (0.41 to 1.04)**	**0.55 (0.33 to 0.93)**	1.17 (0.56 to 2.46)
Depressive symptoms*	2.21 (1.03 to 4.76)	1.68 (0.75 to 3.77)	3.78 (1.43 to 10.04)
Anxiety symptoms†:			
no	1.00 (reference)	1.00 (reference)	1.00 (reference)
light	1.07 (0.72 to 1.58)	1.00 (0.65 to 1.55)	**2.32 (1.17 to 4.62)**
moderate to severe	1.08 (0.51 to 2.31)	1.13 (0.49 to 2.58)	**2.72 (0.89 to 8.30)**
Other psychotropic use	Not applicable	**3.09 (1.87 to 5.10)**	**4.43 (2.49 to 7.85)**
Number of non-psychotropic drugs used:			
0-3	1.00 (reference)	1.00 (reference)	1.00 (reference)
4-6	0.84 (0.53 to 1.32)	1.29 (0.76 to 2.19)	0.64 (0.30 to 1.34)
≥7	1.39 (0.86 to 2.25)	**2.32 (1.34 to 4.01)**	0.56 (0.26 to 1.20)
Frequency of medical visits:			
once a month or more	1.00 (reference)	1.00 (reference)	1.00 (reference)
once every 2 months	0.81 (0.53 to 1.24)	0.77 (0.48 to 1.23)	0.63 (0.31 to 1.27)
3-4 times a year	**0.48 (0.29 to 0.77)**	**0.46 (0.27 to 0.79)**	0.55 (0.23 to 1.31)
less frequently	**0.15 (0.05 to 0.46)**	**0.25 (0.08 to 0.81)**	0.11 (0.01 to 1.04)
Dependency‡:			
no	1.00 (reference)	1.00 (reference)	1.00 (reference)
light	1.47 (0.92 to 2.34)	1.11 (0.66 to 1.86)	0.64 (0.27 to 1.51)
moderate	**2.19 (1.18 to 4.08)**	1.01 (0.50 to 2.03)	1.57 (0.56 to 4.37)
severe	**3.00 (1.05 to 8.60)**	0.47 (0.14 to 1.57)	2.77 (0.62 to 12.47)
Cognitive level:			
normal	1.00 (reference)	1.00 (reference)	1.00 (reference)
Mild Cognitive Impairment	1.72 (0.86 to 3.41)	0.84 (0.38 to 1.84)	**2.57 (0.98 to 6.76)**
dementia	1.27 (0.70 to 2.32)	1.04 (0.54 to 2.01)	0.90 (0.37 to 2.20)
Alcohol consumption:			
no	1.00 (reference)	1.00 (reference)	1.00 (reference)
every day, >3 glasses	0.51 (0.21 to 1.25)	0.67 (0.24 to 1.82)	0.46 (0.07 to 2.87)
every day, ≤3 glasses	1.06 (0.67 to 1.66)	1.27 (0.77 to 2.09)	0.83 (0.40 to 1.72)
at least once a week	1.14 (0.63 to 2.07)	0.90 (0.46 to 1.76)	1.71 (0.70 to 4.21)
less frequently	0.60 (0.22 to 1.65)	0.89 (0.29 to 2.72)	0.90 (0.17 to 4.85)
Tobacco use:			
never	1.00 (reference)	1.00 (reference)	1.00 (reference)
past use	1.14 (0.73 to 1.78)	1.15 (0.70 to 1.89)	0.67 (0.31 to 1.46)
current use	1.19 (0.42 to 3.37)	1.59 (0.55 to 4.60)	0.50 (0.06 to 4.49)

*According to Center for Epidemiologic Studies Depression scale[156] (score ≥17 for men; ≥23 for women).
†According to Spielberger state anxiety scale[195] (≤20 no symptoms; 21 to 35 light symptomatology; ≥36 moderate to severe symptomatology).
‡According to the Rosow-Breslau Functional health scale[196], the Lawton Instrumental Activity of Daily Living (IADL) scale[197] and the Katz Activity of Daily Living (ADL) scale[198] (light if at least one item of Rosow scale is altered, moderate if at least one item of Rosow and IADL scales are altered and severe at least one item of Rosow, IADL and ADL scales are altered.

5.2. Temporal trends of the characteristics associated with psychotropic use: a study using the PAQUID cohort

5.2.1. Context and objective

Several good practice guidelines intended to limit over-consumption of psychotropics in the elderly population have been published during the last decade. Our aim was to evaluate temporal trends associated with psychotropic use (considering the two most often prescribed families, *i.e.* benzodiazepines and antidepressants) in two generations of persons of 75 years and older between 1988-1998 and 2001-2008).

5.2.2. Population, Method

We used the data from the PAQUID cohort previously described. Multivariate logistic regression models were used to identify factors associated with psychotropic use (overall use and main classes) in the two periods.

5.2.3. Main conclusions

Psychotropic use was high in the two periods (prevalence of about 50%) (Table 44). Antidepressant use increased between the two periods, which may be in agreement with the health authority recommendations on the management of depression (Table 44). Benzodiazepine consumption remained high, with no marked changes between the two periods despite good practice guidelines and health authority recommendations (Table 44). Characteristics associated with psychotropic use were the same for both periods (female gender, dementia or depression, dependency in daily activities, polypharmacy) (Table 45 and Table 46: comparison of users and non-users; Table 47 and Table 48: characteristics associated with psychotropic use). The abstract of a manuscript related to these studies and in preparation for submission (Evolution of the characteristics associated with psychotropic use in a French cohort of elderly persons), can be found in Annexes 1.

Table 44. Prevalence of psychotropic use in two generations of persons aged 75 years and older, included in the PAQUID programme, between 1988-1998 and 2001-2008

	Period 1: 1988 to 1998 n=1882 (%)	Period 2: 2001 to 2008 n=1212 (%)
Psychotropic use		
Yes	1022 (54.3)	714 (58.9)
No	860 (45.7)	498 (41.1)
Benzodiazepine use		
Yes	857 (45.5)	564 (46.5)
No	1025 (54.5)	648 (53.5)
Antidepressant use		
Yes	225 (12.0)	340 (28.0)
No	1657 (88.0)	872 (72.0)

Table 45. Comparison of psychotropic users and non-users between 1988 and 1998, among 1882 persons aged 75 years and older, included in the PAQUID programme

	Psychotropic use			Benzodiazepine use			Antidepressant use		
	Yes, n=1022 (%)	No, n=860 (%)	P value	Yes, n=857 (%)	No, n=1025 (%)	P value	Yes, n=225 (%)	No, n=1657 (%)	P value
Polymedication*	180/1022 (17.6)	26/860 (3.0)	$<10^{-3}$	166/857 (19.4)	38/975 (3.7)	$<10^{-3}$	57/225 (25.3)	143/1657 (8.6)	$<10^{-3}$
Single or widowed	651/1022 (63.7)	435/860 (50.6)	$<10^{-3}$	551/857 (64.3)	534/1025 (52.1)	$<10^{-3}$	158/225 (70.2)	933/1657 (56.3)	$<10^{-3}$
Female gender	715/1022 (70.0)	448/860 (52.1)	$<10^{-3}$	607/857 (70.8)	556/1025 (54.2)	$<10^{-3}$	171/225 (76.0)	992/1657 (59.9)	$<10^{-3}$
Dementia	111/1022 (10.9)	36/860 (4.2)	$<10^{-3}$	68/857 (7.9)	52/1025 (5.1)	0.01	55/225 (24.4)	72/1657 (4.3)	$<10^{-3}$
Depressive symptoms†	218/908 (24.0)	72/824 (8.7)	$<10^{-3}$	195/786 (24.8)	96/975 (9.8)	$<10^{-3}$	55/184 (29.9)	225/1575 (14.3)	$<10^{-3}$
Dependency‡	965/1022 (95.0)	713/860 (83.1)	$<10^{-3}$	806/853 (94.5)	866/1022 (84.7)	$<10^{-3}$	215/223 (96.4)	1453/1651 (88.0)	$<10^{-3}$
Schooling duration ≥7 years	574/1022 (56.2)	523/860 (60.8)	0.04	491/857 (57.3)	606/1025 (59.1)	0.42	131/225 (58.2)	966/1657 (57.1)	0.71
Age (years), mean (sd)	82.5 (5.3)	81.3 (4.8)	$<10^{-3}$	82.1 (5.1)	81.4 (4.8)	0.002	83.7 (5.4)	81.3 (4.8)	$<10^{-3}$

*Concomitant use of more than 9 drugs.

†According to Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women).

‡According to the Rosow-Breslau Functional health scale.[196]

Table 46. Comparison of psychotropic users and non-users between 2001 and 2008, among 1212 persons aged 75 years and older, included in the PAQUID programme

	Psychotropic use			Benzodiazepine use			Antidepressant use		
	Yes, n=714 (%)	No, n=498 (%)	p	Yes,n=564 (%)	No, n=648 (%)	P value	Yes, n=340 (%)	No, n=872 (%)	P value
Polymedication*	185/714 (25.9)	41/498 (8.2)	$<10^{-3}$	162/564 (28.7)	59/648 (9.1)	$<10^{-3}$	100/340 (29.4)	110/872 (12.6)	$<10^{-3}$
Single or widowed	503/713 (70.5)	232/417 (55.6)	$<10^{-3}$	395/564 (70.0)	317/546 (58.1)	$<10^{-3}$	255/339 (75.2)	444/747 (59.4)	$<10^{-3}$
Female gender	507/714 (71.0)	282/498 (56.6)	$<10^{-3}$	404/564 (71.6)	385/648 (59.4)	$<10^{-3}$	256/340 (75.3)	533/872 (61.1)	$<10^{-3}$
Dementia	259/714 (36.3)	79/420 (18.8)	$<10^{-3}$	177/564 (31.4)	139/552 (25.2)	0.02	162/340 (47.6)	163/752 (21.7)	$<10^{-3}$
Depressive symptoms†	105/545 (19.3)	24/388 (6.2)	$<10^{-3}$	82/434 (18.9)	43/494 (8.7)	$<10^{-3}$	60/238 (25.2)	65/683 (9.5)	$<10^{-3}$
Dependency‡	618/660 (93.6)	314/417 (75.3)	$<10^{-3}$	487/521 (93.5)	413/528 (78.2)	$<10^{-3}$	293/302 (97.0)	599/746 (80.3)	$<10^{-3}$
Schooling duration ≥7 years	490/714 (68.6)	374/498 (75.1)	0.01	388/564 (68.8)	476/648 (73.5)	0.07	234/340 (68.8)	630/872 (72.2)	0.26
Age (years), mean (sd)	86.0 (4.8)	84.1 (4.9)	$<10^{-3}$	85.9 (4.8)	84.3 (5.0)	$<10^{-3}$	86.6 (4.7)	84.5 (4.9)	$<10^{-3}$

*Concomitant use of more than 9 drugs.

†According to Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women).

‡According to the Rosow-Breslau Functional health scale.[196]

Table 47. Characteristics associated with psychotropic use between 1988 and 1998 in 1882 persons aged 75 years and older, included in the PAQUID programme

	Univariate and Multivariate* (reported when significant) odds ratio (IC95%)		
	Psychotropic users (n=1022) *versus* non-users (n=860)	**Benzodiazepine users (n=857) *versus* non-users (n=1025)**	**Antidepressant users (n=225) *versus* non-users (n=1657)**
Polymedication†	6.86 (4.50 to 10.47) 5.84 (3.75 to 9.09)*	6.24 (4.33 to 8.99) 5.61 (3.78 to 8.33)*	3.59 (2.54 to 5.08) 3.51 (2.42 to 5.10)*
Single or widowed	1.71 (1.43 to 2.06)	1.66 (1.38 to 1.99)	1.83 (1.35 to 2.48)
Female gender	2.14 (1.77 to 2.59) 2.01 (1.62 to 2.49)*	2.05 (1.69 to 2.48) 1.96 (1.58 to 2.42)*	2.12 (1.54 to 2.93)
Dementia	2.79 (1.89 to 4.11) 2.08 (1.23 to 3.49)*	1.61 (1.11 to 2.34)	7.12 (4.85 to 10.47) 5.81 (3.82 to 8.85)
Depressive symptoms‡	3.30 (2.48 to 4.39) 2.76 (2.04 to 3.73)*	3.02 (2.32 to 3.94) 2.54 (1.92 to 3.37)*	2.56 (1.81 to 3.62)
Dependency§	3.85 (2.76 to 5.37) 2.27 (1.59 to 3.25)*	3.09 (2.20 to 4.34) 1.94 (1.35 to 2.79)*	3.66 (1.78 to 7.53) 8.75 (1.19 to 64.13)*
Schooling duration ≥7 years	0.83 (0.69 to 0.99)	0.93 (0.77 to 1.12)	0.99 (0.75 to 1.32) 1.41 (1.03 to 1.91)*
Age	1.05 (1.03 to 1.12)	1.03 (1.01 to 1.05)	1.09 (1.06 to 1.12) 1.06 (1.03 to 1.09)*

†Concomitant use of more than 9 drugs.

‡According to Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women).

§According to the Rosow-Breslau Functional health scale.[196]

Table 48. Characteristics associated with psychotropic use between 2001 and 2008 in 1212 persons aged 75 years and older, included in the PAQUID programme

	Univariate and Multivariate* (reported when significant) odds ratio (IC95%)		
	Psychotropic users (n=714) *versus* non-users (n=498)	**Benzodiazepine users (n=564) *versus* non-users (n=648)**	**Antidepressant users (n=340) *versus* non-users (n=872)**
Polymedication†	3.90 (2.91 to 5.56)	4.02 (2.91 to 5.56) 3.05 (2.13 to 4.36)*	2.89 (2.12 to 3.93) 2.10 (1.50 to 2.94)*
Single or widowed	1.91 (1.49 to 2.46) 1.31 (0.93 to 1.84)*	1.69 (1.32 to 2.16)	2.07 (1.56 to 2.76)
Female gender	1.88 (1.48 to 2.39) 1.47 (1.05 to 2.08)*	1.73 (1.36 to 2.20) 1.67 (1.25 to 2.24)*	1.94 (1.46 to 2.57) 1.78 (1.29 to 2.46)*
Dementia	2.46 (1.84 to 3.28) 1.89 (1.31 to 2.72)*	1.36 (1.05 to 1.77)	3.29 (2.50 to 4.33) 2.70 (2.00 to 3.63)*
Depressive symptoms‡	3.62 (2.27 to 5.76) 3.54 (2.01 to 6.23)*	2.44 (1.65 to 3.63) 1.96 (1.30 to 2.96)*	3.20 (2.17 to 4.73)
Dependency§	4.83 (3.29 to 7.08) 2.54 (1.67 to 3.86)*	3.82 (2.55 to 5.72) 2.54 (1.64 to 3.92)*	7.99 (4.02 to 15.89) 4.56 (2.25 to 9.24)*
Schooling duration ≥7 years	0.73 (0.56 to 0.94)	0.80 (0.62 to 1.02)	0.85 (0.65 to 1.11)
Age	1.09 (1.06 to 1.07)	1.07 (1.04 to 1.10)	1.09 (1.06 to 1.12)

†Concomitant use of more than 9 drugs.

‡According to Center for Epidemiologic Studies Depression scale (score ≥17 for men; ≥23 for women).

§According to the Rosow-Breslau Functional health scale.[196]

PART VI - General discussion

1. Main results

1.1. BENZODEM and BENZODEM2

Both the prospective and retrospective approaches conducted in the PAQUID cohort (BENZODEM, Part III) and the retrospective approach using the Quebec Health Insurance reimbursement data (BENZODEM2, Part IV) concluded that there was an increased risk of dementia associated with benzodiazepine use. The excess risk appeared only when the cumulative duration of exposure exceeded 3 months (BENZODEM2) *i.e.* disrespecting the international recommendations for proper prescription of these drugs.[82] We also highlighted a clear dose-effect relationship (Part IV) and a greater risk in users of molecules with a long elimination half-life, compared to short half-lives (Part IV). The risk associated with benzodiazepine use did not seem to be explained by a protopathic bias, at least for the most part (Parts III and IV). Our results confirmed previous findings but offered a higher level of confidence, mainly due to the care taken to minimise the possibility of a protopathic bias, which was the main limitation of previous studies on the topic (Part II). Table 49 compares the validity of our results to those of the previous studies according to the Newcastle-Ottawa criteria (the process of attributing the stars is described in more detail in Annexes 4). Table 50 compares the confidence of our results to those of the previous studies on the basis of the criteria described in Part II (*i.e.* Newcastle-Ottawa criteria, and the likelihood of results being mainly explained by a protopathic bias).

Table 49. Quality of BENZODEM and BENZODEM2 studies assessed by the Newcastle-Ottawa criteria (in comparison with previous works)

Case-control studies	**Selection** (maximum 4 ⋆)	**Comparability** (maximum 2 ⋆)	**Exposure** (maximum 3 ⋆)	**Total ⋆** (maximum 9 ⋆)
Lagnaoui *et al.* 2002[7]	⋆⋆⋆⋆	⋆⋆	⋆⋆	8
Lagnaoui *et al.* 2009[6]	⋆⋆⋆	⋆	⋆	5
Wu *et al.* 2009[5]	⋆⋆⋆	⋆	⋆⋆	6
Wu *et al.* 2011[8]	⋆⋆⋆	⋆	⋆⋆	6
Gallacher *et al.* 2011[9]	⋆⋆⋆	⋆⋆	⋆	6
Billioti de Gage *et al.* 2012[149]	⋆⋆⋆⋆	⋆⋆	⋆⋆⋆	**9**
Billioti de Gage *et al.* 2014[179]	⋆⋆⋆	⋆	⋆⋆	**6**
Cohort studies	**Selection** (maximum 4 ⋆)	**Comparability** (maximum 2 ⋆)	**Outcome** (maximum 3 ⋆)	**Total ⋆** (maximum 9 ⋆)
Fastbom *et al.* 1998[10]	⋆⋆⋆⋆	⋆	⋆	6
Billioti de Gage *et al.* 2012[149]	⋆⋆⋆⋆	⋆⋆	⋆⋆	**8**

Table 50. Confidence in the results of studies assessing the relation between benzodiazepine use and dementia (Billioti de Gage et *al.*[199])

Study	Dementia risk in benzodiazepine users	Newcastle-Ottawa scale, total ⋆ (maximum quality: 9⋆)	Protopathic bias explaining the results	Confidence in the results
Fastbom *et al.*, 1998[10]	Decreased	6 (cohort study) 7 (case-control study)	likely (because of short follow-up)	low
Lagnaoui *et al.*, 2002[7]	Increased	8 (case-control study)	likely (for ever use and current use estimations) possible (for former use ≥3 year discontinuation)	low average
Lagnaoui *et al.,* 2009[6]	Increased (not significantly)	5 (case-control study)	likely (because of short follow-up)	low
Wu *et al.*, 2009[5]	Increased	6 (case-control study)	likely (in main analysis, time of exposure not taken into account) possible (in sensitivity analysis excluding hypnotics)	low average
Wu *et al.*, 2011[8]	Increased	6 (case-control study)	likely (in analysis considering current use and former use <3 year discontinuation) possible (in former users ≥3 year discontinuation)	low average
Gallacher *et al.,* 2011[9]	Increased	6 (case-control study) 6 (cohort study)	likely (in analyses based on ever users, other analyses inconclusive)*	low
Billioti de Gage *et al.*, 2012[149]	**Increased**	**8 (cohort study)**	**unlikely (delayed increased risk in benzodiazepine initiators)**	**good**
Billioti de Gage *et al.*, 2012[149]	**Increased**	**9 (case-control study)**	**unlikely (analyses based on past initiators)**	**good**
Billioti de Gage *et al.*, 2014[179]	**Increased**	**6 (case-control study)**	**unlikely (recent exposures censored)**	**good**

*Note: subgroup analysis discriminating recent initiators (likely to convey a protopathic bias) and past initiators (unlikely to convey a protopathic bias) were inconclusive because of low sample sizes.

1.2. All studies

Out of the 9 studies conducted[5-10 149 179] seven concluded that there was a statistically increased risk.[5 7-9 149 179] In one other[6] the increased risk was not statistically significant owing to insufficient sample size. The earliest study[10] concluded that there was a paradoxical protective association; it is likely that this was related to misclassification of exposure. Three studies had a low internal validity, making their results less reliable.[6 9 10] Conclusions based upon the studies with the highest levels of confidence (average or good)[5 7 8 149 179] could be the following:

- Exposure to benzodiazepines was found to be associated with an increased risk of dementia (strength of association: 1.24 to 2.30).
- The excess risk appears to be delayed after initiation of the treatment[149] and unlikely for cumulative uses of less than 3 months.[5 8 179]
- This risk increased with cumulative dose or treatment duration[5 8 179] and when molecules with a long half-life were used.[179]
- Reversibility was observed 1 to 2 years after treatment discontinuation,[8] but not with heavy users (>360 DDDs during follow-up).

On this basis, four questions emerge:

- Is a causal link between benzodiazepine use and dementia likely?
- Which populations or user groups are concerned?
- What are the implications for public health and clinical practice?
- Is there other relevant research to be conducted on the topic?

2. Is a causal link between benzodiazepine use and dementia likely?

It would be offensive to consider that an association found by seven studies could be spurious. Sadly however, in observational research, a statistical association does not mean a causal association. Except for particular situations such as a dramatic increase in a risk or some very specific events, causal inference in non-experimental studies is always tricky and prone to generate endless controversies. For example, prescription of benzodiazepine might simply be an early marker of a condition associated with an increased risk of dementia. For example, prescription of benzodiazepines could identify subgroups of individuals with a higher risk of dementia preceded by recurrent episodes of anxiety, insomnia or depression.[62 65 200] In that

event, benzodiazepines would not have any direct effect on the risk of dementia but could be a marker allowing early identification of individuals possibly at risk. This counterargument is a serious contender, even if in seven studies, the association remained significant after adjustment on symptoms that are both indications for prescribing benzodiazepines and risk factors or prodromes for dementia. Moreover, reversed causality remains an alternative explanation for the association found, even if the most recent studies have made valuable attempts to control for this type of bias. Two other limitations may have jeopardised the validity of the results: (1) in several studies putative confounders such as alcohol consumption, educational level, depression, anxiety, insomnia were not controlled for; (2) the criteria used for the diagnosis of the various subtypes of dementia have evolved in recent years, which could raise concerns about case representativeness regarding most recent criteria.

Referring to the pioneering work of Bradford Hill,[201] it is justifiable to consider that five of his nine causality criteria are more or less fulfilled:

- *Consistency.* The association between benzodiazepine consumption and dementia was found statistically significant in seven studies, its strength being roughly of the same order of magnitude even though the studies were conducted by different research teams using different data sources and different approaches.

- *Temporality.* The corner stone for causal inference is that the start of exposure precedes the effect in time. Considering the clinical diagnosis of dementia, this criterion was fulfilled in all the studies. However, owing to the long infra-clinical process of dementia, dating its actual onset is rash to say the least. This limitation was partially circumvented as studies found an association with treatments initiated several years before diagnosis.[7-9 149 179]

- *Biological gradient* is another major argument for causality. A relation between exposure density and the magnitude of the association was sought in four studies,[5 8 9 179] not found in one[9] but present in the others and marked in one.[179] Although convincing, this argument could be questioned since long-term or highly dosed treatments might correspond to the most severe forms of anxiety, sleep disorders or depression, which are both possible prodromes and risk factors for dementia.

- *Plausibility and coherence.* Although no univocal pathophysiological mechanism may be put forward, a deleterious effect of benzodiazepines on cognitive functions (*e.g.* anterograde amnesia[202-205] or long-term cognitive decline[186]) and cognitive reserve

capacity[51] is documented or at least plausible. The association found between benzodiazepines and dementia was not explained by a longitudinal effect of benzodiazepines on cognition (Part V). In the event of a causal role by benzodiazepines, the most plausible explanation would be their deleterious effect on the cognitive reserve abilities.[51] Intellectual stimulation is recognized to be a protective factor for dementia (Part I), probably by increasing brain plasticity. Benzodiazepines could have the opposite effect: their long-term use could lower the mobilization of the cognitive brain reserve, leading to an anticipation of dementia onset. A last explanation, possibly the most plausible one, would be a combination of two mechanisms, (i) causal (deleterious effect on the cognitive brain reserve) accounting for a given part of the association, and (ii) non-causal, for example benzodiazepines being simply a marker allowing early identification of a condition (*e.g.* anxiety, insomnia or depression) making individuals at risk for dementia. It is worth noting that the odds ratio found in the BENZODEM studies for benzodiazepine users not using or not having used other psychotropics, and after adjustment on depressive disorders, was in the order of magnitude of 1.30 or 1.40. In the absence of residual confounding, this value could reflect part of the intrinsic effect of benzodiazepine exposure.

From this assessment, it is sensible to consider that a causal role of benzodiazepines is at least possible, even if criteria such as *strength of association*, *specificity*, *experimental evidence* and *analogy* are not satisfied.

3. Which populations or user groups are concerned?

3.1. Elderly

Most of the studies were conducted among elderly populations, even if inclusions began at 45 years old for Wu *et al.*[5 8] The elderly are indisputably more vulnerable to neurocognitive side effects and benzodiazepines could impair their cognitive reserve capacity, thus reducing their ability to cope with early brain lesions. Therefore, no conclusions can be drawn concerning a possible excess risk for younger populations.

3.2. Long-term users

It is sensible to conclude that the deleterious effect of benzodiazepines is to be feared only for long-term uses. Indeed, Billioti de Gage *et al.*[179] found no increased risk for cumulative uses of 3

months or less and Wu *et al.*[8] showed that symptoms regressed after discontinuation only when the treatment was short and not when it was long.

3.3. Benzodiazepine-related drugs

Since benzodiazepines and related compounds *e.g.* zolpidem, zopiclone and zaleplon were generally pooled in the exposure definition, no conclusion can be drawn about the relative toxicity of the latter. As related drugs are mostly short-acting molecules, sharing similar properties to benzodiazepines, it is sensible to consider that they would fall into the same category of risk as short-acting benzodiazepines, *i.e.* lower than for long-acting molecules.[179]

4. What are the implications for public health and clinical practice?

4.1. What would be the consequences in the event of a causal path?

Concluding that benzodiazepines, at least their long-term use, could increase the risk of dementia by a factor of 1.5 or 2 would have tremendous consequences in terms of public health and economic burden. Their use is constantly high in the elderly, ranging between 7% and 43% across countries,[111 206-208] and is often chronic and seldom justified. Considering both the figures for the incidence of dementia and the prevalence of long-term benzodiazepine use in various countries leads to estimates of several thousands of cases in excess per year in a country such as France.

4.2. What to do with this knowledge?

Benzodiazepines remain valuable tools for managing anxiety and insomnia, but what is known about their effects on cognition (*e.g.* short-term effects on memory, putative increased risk of dementia for the long-term) and the precautionary principle both suggest that their use should be restricted to treatments of short duration and only those that are fully justified. There is currently no evidence of an increased risk for uses that comply with international guidelines *i.e.* not exceeding one month for hypnotics and three months for anxiolytics. Consequently, it seems crucial to carefully balance benefits and risks when renewing a treatment; abrupt discontinuation of long-term treatments should be avoided, owing to the risk of withdrawal effects.

4.3. What has already been done?

Before the publication of the BENZODEM programme, our expertise in the field was solicited by the French Health Ministry. On the eve of this publication, different press releases were launched by the French health authorities concerning good practices for prescription of hypnotics in the elderly and measures aiming to fight benzodiazepine misuse. They planned: (i) analysis of scientific data (reports on benzodiazepine consumption in France, critical review of the studies conducted on benzodiazepines and dementia, including our own works), (ii) to refer the matter of the relationship between benzodiazepine use and dementia to the European Medical Agency in order to debate whether a change in the Summary of the Product Characteristics was justified, (iii) to modify access to benzodiazepines (secured prescriptions, smaller sizes of packaging), (iv) communication toward health professionals. Links to these press releases are provided in Annexes 3.

After the BENZODEM study was published in September 2012, the possibility (if not plausibility) of a link and its potentially huge impact on the elderly if this link was proven, led to information being widely disseminated to health professionals (general practitioners and psychiatrists) with the aim of (i) reminding them of good prescription practices, and (ii) drawing their attention to possible risks associated with long-term use of benzodiazepines. The letter sent to health professionals is provided in Annexes 3. In July 2014, before the publication of the BENZODEM2 study, the French health authorities decided to lower the reimbursement rate for benzodiazepines indicated as hypnotics.

4.4. Other perspectives: how to improve monitoring of cognitive side effects of drugs?

In September 2014, an editorial published by two US researchers[209] which accompanied the publication of BENZODEM2, underlined a failure in identifying and monitoring putative cognitive side effects of drugs. They suggested developing "*a structured reproducible approach to the identification and accurate monitoring of the adverse cognitive effects of all drug treatments used by older adults with multiple chronic conditions, particularly by those at risk of Alzheimer's disease".* This approach could be based on linking *"the multiple data provided by a growing number of electronic medical record systems".* This *"could improve therapeutic decisions among doctors treating high risk older adults with multiple chronic conditions and eventually help to reduce the burden of cognitive decline worldwide".*

5. Is there other relevant research to be conducted on the topic?

Further studies should evaluate the risk of treatments initiated in younger persons. However, designing such a study would be challenging since it would require an unusually long follow-up (at least 30 years) with regular collection of validated information about drug exposure, cognitive status (including a robust dementia diagnosis), dementia prodromes and risk factors.[138-140]

Animal or cellular models would also be needed to help in identifying neurobiological mechanisms linking benzodiazepines with the risk of Alzheimer's disease. Moreover, this approach, if conclusive, would be a major argument for drug causation.

6. Summary

Careful assessment of data in the literature and our study programmes (*i.e.* BENZODEM and BENZODEM2) pointed to the existence of a 1.5- to 2-fold increased risk of dementia following the long-term use of benzodiazepines by the elderly. At this stage, the causal nature of this association is far from being established, but could at least be considered possible. A major finding is that treatments respecting recommended durations of use would not be concerned. These two points make it crucial to avoid unjustified initiation and uncontrolled chronic use.

GENERAL CONCLUSION

Our research programme, including the BENZODEM and BENZODEM2 publications and five complementary studies (not all presented in the present document) reinforced the suspicion that there was an increased risk of dementia associated with benzodiazepine use. Obviously, despite our step-by-step approach using a specifically designed study or analysis in every instance, the causal character of this association remains unproven. However, some arguments plead in favour of an association that is not explained or not only explained by residual confounding or reverse causality bias:

- First, this deleterious effect of benzodiazepines can be qualified as biologically plausible when referring to the well-established effects of these drugs on memory and cognition.

- In the prospective approach taken by BENZODEM, the excess risk did not appear immediately after exposure start, which would suggest a protopathic bias, but after a delay of 5-7 years. This was confirmed by the approach using subsequent cohorts which did not find a significant association for recent initiators.

- This model which concluded in a significant association was adjusted on all the covariates known or suspected to be potential confounders (except education level in BENZODEM2).

- Supplementary adjustment on depression (BENZODEM) and depression, anxiety and sleep disorders (BENZODEM2), which are suspected to be both prodromes and/or risk factors for dementia, did not significantly alter the results.

- Even when an association was also found between antidepressants and dementia, the association with benzodiazepines persisted, although it was weaker, in patients using benzodiazepines alone.

- The strength of association increased with the density of exposure and the elimination half-life of the molecule used (BENZODEM2).

- The results of BENZODEM and BENZODEM2 were consistent with those of previous studies having used different approaches and with samples from different populations with different benzodiazepine consumption habits.

At this stage, even if the causal nature of this association is far from being established, it should be considered as at least possible if not plausible. Here we touch on the main lesson of this

never-ending story: as the incidence of dementia and benzodiazepine use are both quite high, particularly in the elderly, even a moderate increase in this risk would result in a tremendous number of cases in excess and would have a major public health impact. An important finding of BENZODEM2 is that treatments respecting recommended durations are not at risk and the body of evidence appears sufficient to apply the precautionary principle: **not fully justified and long-term use of benzodiazepines should be cautioned against**.

Considering the extent to which benzodiazepines are prescribed and the other adverse effects of this drug class, our results should provide incentives for clinicians to respect regulations concerning benzodiazepine prescriptions.

Obviously, further studies would be needed to identify the mechanism of this association and to better understand the role of associated symptoms such as sleep disorders, anxiety and depression. However, such further developments were beyond the scope of this thesis.

FRENCH SUMMARY

1. Présentation du travail (Introduction et Partie I)

1.1. Contexte et objectifs de la thèse

Les benzodiazépines sont des médicaments psychotropes essentiellement utilisés pour leurs effets anxiolytiques et hypnotiques.[82] Leur consommation est particulièrement élevée chez les femmes et les personnes âgées.[207] La réglementation Française à l'instar de la plupart des pays industrialisés suggère des indications spécifiques et des utilisations de courte durée (n'excédant pas quelques semaines ou mois), particulièrement du fait du risque de syndrome de sevrage rendant l'interruption du traitement difficile.[82] De plus, ces médicaments se caractérisent par un épuisement de leur effet à long terme.[77] Malgré cela, le recours à ces médicaments est bien souvent chronique particulièrement chez les sujets âgés chez lesquels des durées de plusieurs années sont fréquemment observées.[207 210] Chez les personnes âgées, outre le risque de chutes et de fractures,[76] les effets délétères des benzodiazépines sur la mémoire et la cognition[135 202 211 212] sont particulièrement préoccupants compte tenu de leur plus grande vulnérabilité neurocognitive.[134]

La démence se caractérise par une détérioration graduelle et irréversible des fonctions cognitives. La maladie touche 36 millions de personne dans le Monde.[3] Elle constitue la principale cause d'invalidité aux âges élevés de la vie et participe à un fardeau sociétal appelé à devenir de plus en plus préoccupant du fait du vieillissement de la population.[3 4] Comme cette maladie ne bénéficie pas à l'heure actuelle de traitement curatif, il paraît crucial d'identifier et d'agir sur les facteurs de risque modifiables. Dans ce contexte, nous nous sommes intéressés à la consommation de benzodiazépines. D'une part, car elles constitueraient un facteur de risque possible de la maladie compte tenu de leurs effets délétères sur la cognition connus à court terme,[135 138 211] plus controversés sur le long terme.[137] D'autre part, parce qu'une association de type causal entre benzodiazépines et démence aurait un impact dramatique en terme de nombre de nouveaux cas en excès (du fait des prévalences très élevées de l'usage des benzodiazépines et de la démence chez les sujets âgés) avec des conséquences catastrophiques du fait de la sévérité et des coûts engendrés par cette maladie.[3]

L'objectif principal de ce travail était d'étudier la relation entre consommation de benzodiazépines et risque de démence chez la personne âgée. Nous avons d'abord réalisé une revue de la littérature dans le but d'identifier les travaux préexistant sur le sujet et de faire un bilan des connaissances (Partie II). Ces études se heurtant à des difficultés méthodologiques non résolues, nous avons cherché à réévaluer la relation entre benzodiazépines et démence d'abord en utilisant les données issues d'une cohorte en population (PAQUID, Partie III), puis en utilisant

les informations issues de la base de données de remboursement de la Régie de l'Assurance Maladie du Québec (RAMQ, Partie IV). Quelques questions émergeant des travaux sur PAQUID et la RAMQ ont donné lieu à des études supplémentaires (Partie V). L'ensemble des travaux réalisés nous a conduit à émettre des arguments concernant la question de la possibilité d'une relation de type causal entre consommation de benzodiazépines et risque de démence et de ses conséquences pour la santé publique (Partie VI).

1.2. En quoi la recherche d'un lien entre la consommation de benzodiazépines et risque ultérieur de démence est-elle rendue complexe ?

Etudier la relation entre la consommation de benzodiazépines et la démence relève d'un véritable défi méthodologique. Premièrement, un essai clinique avec tirage au sort étant éthiquement inacceptable, répondre à la question d'un possible lien de cause à effet n'est possible que par le biais d'études observationnelles ce qui signifie que leurs résultats seront toujours mis en doute dès qu'il s'agit de répondre en termes de causalité. Deuxièmement, compte tenu de la longue phase de latence infra-clinique de la démence (10 ans ou plus bien que non encore parfaitement connue, ce qui élève encore le niveau de complexité), une étude cherchant à évaluer la possibilité d'un lien causal devrait considérer des variables comme l'exposition médicamenteuse ou les facteurs de risque plus d'une décennie avant le diagnostic de la maladie ce qui demande de disposer d'un très long suivi, ce qui n'est pas aisé, surtout dans une population âgée. Troisièmement, malgré certaines contradictions, les données de la littérature indiquent une prévalence plus élevée de symptômes de type anxiété, dépression ou insomnie dans les années précédant le diagnostic de démence ou en association avec le diagnostic de *Mild Cognitif Impairment* (MCI).[29 139 140] Malheureusement, l'état actuel des connaissances ne permet pas de déterminer une limite chronologique précise en deçà de laquelle de tels symptômes seraient trop précoces pour être considérés comme des prodromes de la maladie. Cette question est majeure puisque ces symptômes correspondent aux principales raisons de prescrire des benzodiazépines. Conclure à une association entre consommation de benzodiazépines et démence indépendamment d'un biais protopathique (les benzodiazépines n'étant pas la cause de la maladie mais prescrites en raison de ces signes avant-coureurs) s'avère donc délicat. Quatrièmement, la force de l'association attendue est faible et atteindre la significativité statistique après avoir considéré l'ensemble des facteurs de confusion potentiels est problématique à moins de disposer d'échantillons de tailles considérables.

L'approche observationnelle (seule faisable) la plus parfaite possible exigerait donc (en dehors d'un protocole très abouti) :

- Une grande taille d'échantillon pour disposer de la puissance statistique suffisante pour étudier la force de l'association pour différents profils d'utilisation, différents types de benzodiazépines et l'influence de certains « facteurs de risque ».

- Un suivi très prolongé (idéalement plus de 15 ans) pour tenir compte de la phase de latence de la démence. Minimiser le biais protopatique suppose en effet de s'intéresser aux sujets ayant débuté leur traitement sans que l'on puisse soupçonner qu'il ait été motivé par des prodromes précoces de la maladie (anxiété, dépression, troubles du sommeil).

- Un niveau d'exposition aux benzodiazépines suffisant dans la population source de l'échantillon avec une grande variété de types d'exposition (exemple : durée, types de molécules) pour étudier la force de leur association avec la survenue d'une démence.

- Un échantillon représentatif de la population générale pour rendre l'extrapolation des résultats et conclusions peu critiquables.

- Un diagnostic fiable et reproductible de la démence (et si possible des différents types de démence ayant certainement des mécanismes physiopathologiques et des facteurs de risque distincts).

- Une fiabilité et une description précise de l'exposition aux benzodiazépines, et ce pour tous les sujets et tout au long du suivi.

- Une faible proportion de perdus de vue et une documentation des causes d'arrêt de suivi, ceci pour minimiser les biais de sélection et celui de déplétion des sujets à risque.

- Une documentation précise et fiable, pour tous les sujets, des pathologies intercurrentes, des éventuels facteurs de risque de démence ou des facteurs pouvant être protecteurs ainsi que de toutes les caractéristiques et variables pouvant avoir un intérêt pour juger de la comparabilité des groupes et permettre la neutralisation d'éventuelles différences de répartition (par ajustement, score de propension, etc.).

- Des tests fiables, pratiqués de manière répétée et rapprochée sur l'ensemble des sujets tout au long du suivi pour renseigner le niveau des fonctions cognitives (tests psychométriques évaluant l'ensemble des capacités cognitives (MMSE), celui des facultés cérébrales plus spécifiques (fluidité verbale, fonctions visuo-spatiales, mémoire visuelle, etc.), et le niveau d'anxiété, de troubles du sommeil et de symptômes dépressifs.

2. Revue de la littérature (Partie II)

2.1. Objectif

Avant la réalisation d'une nouvelle étude, l'approche rationnelle consistait, du fait du large matériau de travail déjà existant, à demander à un groupe d'experts de coter le niveau d'évidence de l'association causale entre benzodiazépines et risque de démence. Le budget nécessaire à une telle expertise, pourtant limité, n'ayant pu être dégagé, ce travail a été entrepris, sous une forme différente, au cours de cette thèse. Une revue de la littérature a permis d'évaluer la qualité des connaissances sur le sujet et d'envisager de nouvelles études si le niveau de crédibilité des résultats était insuffisant.

2.2. Méthode

Une recherche dans la base de donnée Medline a été réalisée de façon à identifier l'ensemble des études observationnelles sur le sujet. Le niveau de qualité de ces études a ensuite été évalué en utilisant l'échelle de Newcastle-Ottawa[142] considérée comme l'un des outils les plus efficaces pour évaluer spécifiquement la qualité des études observationnelles.[141]

2.3. Résultats

2.3.1. Description des études

La recherche a permis d'identifier six études publiées entre 1998 et 2011 (Tableau 9). Ces études sont résumées dans le Tableau 10 et seront brièvement présentées par ordre chronologique.

2.3.1.1. Etude de Fastbom *et al.*, 1998

Le premier travail réalisé sur le sujet a été publié par Fastbom *et al.*[10] en 1998. Les auteurs s'étaient intéressés au rôle des récepteurs GABA dans les mécanismes de neuroprotection et, à l'opposé des effets délétères des benzodiazépines, recherchaient leur rôle bénéfique sur le risque de démence. Leur étude a été conduite sur la cohorte Kungsholmen qui avait inclus en 1987 un échantillon aléatoire de sujets de 75 ans et plus, institutionnalisés ou non, et sélectionnés parmi les habitants d'une paroisse de Stockholm (Suède). A la fin des 3 années de

suivi, 75 utilisateurs chroniques de benzodiazépines ont été comparés à 167 « non-utilisateurs » à la date de mesure de l'événement (démences de type Alzheimer et vasculaire). Les auteurs ont conclu à un risque protecteur significatif des benzodiazépines vis-à-vis du risque de démence. Cet effet qui apparaitrait paradoxal aujourd'hui pouvait être en partie expliqué par l'inclusion des anciens et des nouveaux consommateurs de benzodiazépines dans le groupe des non-utilisateurs. En effet, le fait d'arrêter ces médicaments pouvait être justifié par le début de la maladie. Plusieurs études résumées ci-dessous ont conclu que l'augmentation du risque de démence concernait précisément les anciens utilisateurs de benzodiazépines. De même, les nouveaux utilisateurs de benzodiazépines pouvaient voir leur risque augmenté si l'initiation du traitement était liée aux premiers signes de la maladie (anxiété, dépression ou insomnie).

2.3.1.2. Etude de Lagnaoui *et al.*, 2002

La première étude recherchant spécifiquement l'effet délétère des benzodiazépines sur le risque de démence a été publiée par Lagnaoui *et al.* en 2002.[7] Une étude cas-témoins a été conduite dans la cohorte PAQUID constituée par 3777 sujets de 65 ans et plus, non institutionnalisés, sélectionnés aléatoirement à partir des listes électorales de Gironde et Dordogne, deux départements du Sud-Ouest de la France, entre 1987 et 1989. A l'issue des 8 années du suivi, 150 sujets atteints de démence quel que soit le type (cas) ont été appariés et comparés à 3519 sujets non atteints de la maladie (témoins) vis-à-vis de leur exposition antérieure aux benzodiazépines. L'exposition aux médicaments et les fonctions cognitives (dont la démence avec un diagnostic robuste confirmé par un neurologue-gériatre expérimenté), étaient évaluées aux cours de suivis multitransversaux tous les 2-3 ans. Le risque de démence apparaissait augmenté chez les anciens utilisateurs (définis pas un arrêt du médicament au moins 2-3 ans avant le diagnostic de démence) par rapport aux non-utilisateurs (pas de consommation avant la date du diagnostic du cas apparié). Le rapport de cotes ajusté (RC) était de 2,3 (IC95 % 1,2-4,5). Les auteurs ne retrouvaient pas d'excès de risque chez les personnes qui utilisaient encore le médicament à la date de la démence ou moins de 2-3 ans avant. On ne peut exclure que l'association retrouvée chez les anciens utilisateurs soit en partie expliquée par l'arrêt du traitement face à des signes de déclin cognitif ou à des symptômes en lien avec une démence non encore diagnostiquée. De plus, le groupe des utilisateurs en cours (*current users*) regroupait des sujets pouvant avoir des caractéristiques différentes vis-à-vis du risque de développer la maladie: (i) prescriptions récentes possiblement induites par des signes précoces de la maladie (anxiété, dépression, insomnie), potentiellement à l'origine d'un biais protopathique, (ii) initiation récente non liée aux premiers signes de la démence, (iii) utilisateurs chroniques du médicament *a priori* les plus à risque de manifester la maladie. L'absence d'association chez les

utilisateurs « en cours » pourrait s'expliquer par: (i) un biais de déplétion des sujets à risque (le traitement ayant pu être interrompu en raison de troubles cognitifs ou de manifestations précoces de démence, déplétant ce groupe d'utilisateurs de ses sujets « à risque », (ii) une proportion importante de sujets ayant initié récemment leur traitement et pour lesquels le suivi disponible était trop court pour mettre en évidence un éventuel excès de risque de démence.
Enfin, le programme PAQUID ne contenait pas d'information sur les doses et les durées de prescription, deux paramètres importants pour l'identification de profils d'utilisation à risque (usage chronique, épisodique etc.).

2.3.1.3. Etude de Lagnaoui *et al.*, 2009

Sept années plus tard (2009), Lagnaoui *et al.*[6] publient une autre étude cas-témoins nichée dans un échantillon représentatif de 3903 femmes de 65 ans et plus vivant (communauté ou institution) dans la province de la ville de Québec au Canada et ayant été incluses dans l'étude *Canadian Study of Health and Ageing* (CSHA) en 1991-1992. L'objectif était d'évaluer la relation entre consommation de benzodiazépines et risque de démence ou de *Cognitive Impairment No Dementia* (CIND) mesuré durant les 5 ans suivant l'inclusion. Parmi les 510 femmes incluses, 73 (14.3 %) cas (c'est à dire 14 démences et 59 CIND) ont été comparés à 437 témoins (non atteintes de ces maladies) vis-à-vis de leur exposition antérieure aux benzodiazépines (ou apparentés) enregistrée dans la base de données de remboursement de la Régie de l'Assurance Maladie du Québec (RAMQ). Comme dans leur précédente étude,[7] les auteurs concluent à un risque majoré d'altération cognitive (démence ou CIND) chez les utilisatrices ayant arrêté leur traitement plus d'une année avant le diagnostic de la maladie. Compte tenu du nombre limité de cas, cette augmentation n'était pas statistiquement significative (RC 1,5 ; IC95 % 0,6-3,4). Les auteurs ne retrouvaient pas d'augmentation du risque chez les utilisateurs « en cours » (définis par au moins un remboursement retrouvé dans l'année précédant la date du diagnostic). La même remarque que pour l'étude précédente pouvait être faite concernant la définition des profils d'exposition. De plus cette étude souffrait de trois autres limites : (i) la définition des cas mélangeait deux entités (démence et CIND) ayant probablement des mécanismes physiopathologiques différents (ii) les possibles prodromes de la démence (comme la dépression, l'anxiété ou l'insomnie) n'étaient pas pris en compte (par exemple, par une mesure d'interaction ou un ajustement), et (iii) la durée de suivi (2 à 5 ans) restait courte au regard de la période de latence de la maladie supposée être nettement plus longue.

2.3.1.4. Etude de Wu *et al.*, 2009

En 2009 Wu *et al.*[5] publient les résultats d'une étude cas-témoins menée sur un échantillon aléatoire (1 %) de la base de données de remboursement de l'assurance maladie de Taïwan (National Health Insurance Research Database, NHIRD) regroupant environ 97 % (22 millions) de la population Taïwanaise. 779 sujets avec un diagnostic de démence (de tous types) entre 2000 et 2004, âgés de 45 ans et plus (âge moyen : 76 ans), et suivis de 4 à 8 ans ont été inclus dans l'étude. Ces cas ont été appariés avec 4626 témoins non atteints de démence, de même sexe et de même âge. Les auteurs ont conclu à un risque augmenté de démence chez les utilisateurs de benzodiazépines. Comparés à des expositions cumulées de moins 90 *Defined Daily Doses* (DDDs ou doses quotidiennes standard), les longues durées d'utilisation et les fortes densités d'exposition étaient associées à un risque plus élevé de démence (ex : RC 1,38 ; IC95 % 1,03-1,83 pour une durée cumulée de 90 à 179 jours, et 1,45 (1,18-1,79) pour 180 jours et plus). La possibilité de biais protopathique ne pouvait être exclue puisque les initiations récentes et passées n'étaient pas analysées séparément. Les auteurs avaient évalué l'influence possible de ce biais par une analyse de sensibilité consistant à exclure du groupe exposé les utilisateurs de zopiclone et de zolpidem (majoritairement prescrits contre l'insomnie), ce qui ne modifiait pas les résultats.

2.3.1.5. Etude de Wu *et al.*, 2011

En 2011 Wu *et al.*[8] publient une seconde étude cas-témoins en utilisant la *Longitudinal Health Insurance Database* (LHID), un échantillon représentatif d'un million d'individus sélectionné aléatoirement parmi les sujets enregistrés sur la NHIRD décrite précédemment. Les sujets étaient âgés de 45 ans et plus et suivis au maximum durant 11 ans entre 1997 et 2007 (suivi moyen : 9,1 ans). Un grand nombre de cas (8434 de démences de tous types) ont été identifiés et appariés avec 16 706 témoins (non atteints de la maladie) de même sexe, âge et durée de suivi. Cas et témoins ont été comparés vis-à-vis de l'usage « en cours » de benzodiazépines (remboursement au cours des 15 jours précédant la date du premier diagnostic de démence enregistré dans la base) et de l'usage « ancien » (traitement arrêté 16 jours à 1 an, 1 à 2 ans, 2 à 3 ans, et plus de 3 ans avant cette date) à des non-utilisateurs au cours du suivi. Ils ont également considéré les densités cumulées d'exposition durant le suivi (1 à 89 DDDs, 90 à 359 DDDs et 360 DDDs et plus). Après prise en considération des principaux facteurs de risque associés à la prise de benzodiazépines et à la démence (dont des prodromes potentiels tels que l'anxiété, la dépression et l'insomnie), les auteurs concluaient que les utilisateurs « en cours » (quelle que soit la densité cumulée) présentaient un risque plus élevé de démence (RC 2,71 ; IC95 % 2,46-2,99) que des non-utilisateurs (référence) et que les utilisateurs « anciens ». Pour

ce dernier groupe, le rapport de cotes diminuait significativement avec le délai suivant l'arrêt : 1,68 pour moins d'un 1 an ; 1,23 pour 1 à 2 ans ; 1,22 pour 2 à 3 ans et 1,08 pour plus de 3 ans. A partir de ces résultats, les auteurs suggéraient que l'association pouvait être réversible pour les utilisateurs à court terme (1 à 2 ans après l'arrêt pour des densités d'exposition de 1 à 89 DDDs) et pour les utilisateurs à moyen terme (2 à 3 ans après l'arrêt pour des densités cumulées de 90 à 359 DDDs) mais pas pour les utilisateurs à long terme (≥ 360 DDDs). Pour ces derniers, le risque de démence restait significativement augmenté de 65 % plus de 3 ans après l'arrêt des benzodiazépines. Malgré le long suivi disponible, la possibilité de biais protopathique ne peut être écartée car la méthode utilisée n'excluait pas les sujets pour qui les benzodiazépines pouvaient avoir été prescrites en raison de signes précoces de démence comme le suggère les valeurs élevées des rapports de cotes retrouvés chez les utilisateurs « en cours » incluant par définition des initiateurs récents. L'expression de ce biais semblait toutefois moins probable et les résultats plus convaincants dans le groupe des utilisateurs « passés » ayant arrêté leur traitement plus de 3 ans avant la maladie particulièrement pour ceux ayant les densités d'exposition les plus élevées (≥ 360 DDDs). Cette étude était la première à mettre en évidence une relation dose-effet et à rechercher la possibilité de récupération des facultés cognitives après l'arrêt du traitement.

2.3.1.6. Etude de Gallacher *et al.*, 2011

La même année, Gallacher *et al.*[9] publiaient une étude cas-témoins utilisant les données de l'étude prospective Caerphilly. Entre 1979 et 1983, environ 3000 hommes de 40 à 63 ans nés à Caerphilly, petite ville du sud du Pays de Galles représentative de la population masculine de cet âge dans cette zone géographique, ont été inclus et examinés à des intervalles de 5 à 6 ans. A la date de visite la plus récente, 1134 hommes (69,4 % des survivants) avec des durées de suivi de 19 à 24 ans (moyenne 22 ans) étaient éligibles pour l'étude. 93 hommes atteints de démence (vasculaire ou non-vasculaire) ont été comparés à 866 sujets non atteints de cette maladie vis-à-vis de l'utilisation de benzodiazépines. Les auteurs concluaient à un risque augmenté de démence chez les utilisateurs toutes catégories (RC toute démence 3,10 ; IC95 % 1,33-7,23 / RC démence vasculaire 3,24 ; IC95 % 0,98-10,72 / RC démence non-vasculaire 3,34 ; IC95 % 1,10-10,18). L'ajustement sur anxiété et troubles du sommeil ne modifiait pas sensiblement les résultats. Les auteurs ne mettaient pas en évidence de relation dose-effet. L'association la plus forte se manifestait chez les hommes traités pour une durée cumulée estimée de moins de 4 ans (RC 4,38 ; IC95 % 1,15-16,75) mais l'association restait élevée, bien que non statistiquement significative, chez les sujets traités durant des durées cumulées estimées de 4 ans et plus (RC 2,31 ; IC95 % 0,74-7,20). De façon intéressante, le rapport de cotes était de 4,19 (non

significatif, IC95 % 0,90-19,49) dans le petit groupe de sujets ayant commencé leur traitement 13 à 22 ans avant le début de la démence de type non-vasculaire mais plus faible pour les initiateurs plus récents (RC 2,03 ; IC95 % 0,38-10,75). Le contraire était observé pour la démence vasculaire où les rapports de cotes (non significatifs) étaient plus faibles pour les initiations anciennes que pour les récentes : 1,45 (0,13-16,27) et 4,25 (0,94-19,17), respectivement. L'indéniable valeur ajoutée de cette étude était sa très longue durée de suivi permettant d'explorer l'effet des traitements initiés longtemps avant le début de la maladie, une bonne façon de prendre en compte le biais protopathique. Malheureusement, l'échantillon limité et la faible prévalence d'usage des benzodiazépines au sein de cette population masculine du Royaume-Uni limitaient la puissance statistique pour les analyses en sous-groupes dont la plus pertinente, celle visant à évaluer l'influence d'un biais protopathique.

2.3.2. Qualité des études

Les six études avaient une bonne validité sur la base des critères de Newcastle-Ottawa (voir Tableau 11 et Annexes 4) et étaient en général peu critiquables vis-à-vis de la possibilité de biais de sélection. La moindre robustesse de la définition des cas de démence dans les études utilisant des bases de données administratives[5 8] était la seule limite concernant ce biais. Les critiques concernaient plutôt des carences dans l'ajustement, particulièrement sur le niveau d'études[5 8] dans les études sur base de données ou les facteurs de risque de démence très associés aux motifs de prescription des benzodiazépines[6 10] (anxiété, dépression ou insomnie). Les limites concernant la définition de l'exposition étaient celles des études sur base de données ne permettant pas de savoir si les médicaments remboursés ont réellement été consommés par les patients[5 6 8] ou une description insuffisante de la manière dont l'exposition a été recherchée.[9] Pour les études non réalisées sur base de données, les critiques portaient sur l'absence d'information sur les taux de perdus de vue ou de non-réponse et/ou sur leur répartition (différentielles ou non) entre groupes comparés dont les caractéristiques n'étaient pas toujours décrites.[6 7 9 10] Une limite majeure, malheureusement non-évaluée par les critères de Newcastle-Ottawa relatifs aux études cas-témoins (la majorité des études), était, pour certaines études, le suivi insuffisant au regard de la période de latence de la maladie, et la possible influence d'un biais protopathique sur les résultats.[6 7 10]

2.4. Discussion : crédibilité des résultats

La plupart des études (5 sur 6) concluaient à un risque de démence augmenté chez les utilisateurs de benzodiazépines.[5-9] Dans l'une d'elle, l'association n'était pas statistiquement significative.[6] Une étude concluait de façon paradoxale à un effet protecteur.[10] Deux critères ont permis d'évaluer le degré de confiance des résultats : (i) le score obtenu à l'échelle de Newcastle-Ottawa (faible qualité si le score était inférieur à 6, bonne qualité à partir de 6), (ii) la plausibilité d'un biais protopathique (probable, possible, peu probable), non évaluée par l'échelle de Newcastle-Ottawa. Trois nivaux de crédibilité des résultats sur la base de ces deux critères ont été établis : (i) faible degré de confiance (faible qualité, biais protopathique probable ou possible), (ii) degré de confiance moyen (bonne qualité, biais protopathique possible), (iii) bon degré de confiance (bonne qualité, biais protopathique peu probable). De cette évaluation, il ressortait que le niveau de confiance était moyen pour trois études[5 7 8] et bas pour les trois autres.[6 9 10] Aucune ne pouvait justifier d'un bon niveau de confiance, en particulier du fait de la possibilité d'un biais protopathique (Tableau 12).

2.5. Résumé, conclusion

La nature (causale ou non) de la relation entre consommation de benzodiazépines et démence identifiée par 5 des 6 études sur le sujet demeurait incertaine :

- d'une part du fait d'un contrôle insuffisant du biais protopathique,
- d'autre part du fait d'un manque de démonstration d'une relation dose-effet qui serait un argument causal fort.

La conclusion de cette revue soulignait la nécessité de nouvelles études qui réévalueraient l'association entre consommation de benzodiazépines et démence en tenant compte des limites mentionnées ci-dessus.

3. Programme d'études BENZODEM sur la cohorte PAQUID (Partie III)

3.1. Objectif

Afin de réévaluer l'association entre consommation de benzodiazépines et risque de démence en prenant le mieux possible en compte le risque de biais protopathique, le programme

BENZODEM a associé plusieurs études de méthodologies originales et complémentaires (2 études de cohortes, 1 étude cas-témoins).

3.2. Population d'étude

Le projet BENZODEM a été mené sur la cohorte populationnelle PAQUID précédemment citée et développée afin d'étudier le vieillissement cérébral normal et pathologique. Ce programme a permis de recueillir un grand nombre d'informations notamment sur les habitudes de vie, l'état de santé des patients avec les consommations médicamenteuses, la cognition et une recherche systématique des cas de démence. Les sujets étaient issus d'une population générale. Le programme d'étude PAQUID a été décrit précédemment.[147] Le suivi disponible au moment de notre étude était de 20 ans, *a priori* suffisant au regard de la longue période de latence de la maladie pour étudier l'association entre consommation de benzodiazépines et la démence.

3.3. Etudes de cohorte

3.3.1. Méthode

3.3.1.1. Schéma d'étude

Un premier programme d'études prospectives exploitait les 20 ans du suivi de PAQUID. En effet, l'intérêt majeur de PAQUID pour notre objectif d'étude était son suivi exceptionnellement long pour une population âgée associé à un diagnostic très valide des cas de démence. Une période de pré-inclusion de 5 ans a été introduite de façon à contrôler l'état cognitif des sujets avant l'inclusion (absence de démence, même niveau de déclin cognitif entre groupes comparés) et d'exclure les consommateurs prévalents de benzodiazépines.

Dans une première approche, nous avons mené une analyse de survie sur les 15 ans restant. Les sujets ayant initié un traitement par benzodiazépines à la fin de cette période de pré-inclusion ont été comparés à des sujets non-exposés :

- D'une part, vis-à-vis du risque ultérieur de démence évalué par un modèle de Cox ajusté sur les principaux facteurs de confusion (sexe, âge, déclin cognitif avant la première exposition, niveau d'étude, statut marital, facteurs de risque cardiovasculaires) avec une analyse de sensibilité pour la dépression dont le lien avec la démence (facteur de risque ou prodrome) est controversé.[65]

– D'autre part, vis-à-vis du délai de survenue de démence en faisant l'hypothèse que si un excès de risque apparaissait chez les exposés dans des délais courts, il était possible qu'il soit expliqué par un biais protopathique, cette hypothèse devenant moins crédible si l'excès de risque apparaissait au terme d'un long délai depuis l'initiation du traitement.

Une seconde approche a consisté à pooler les résultats issus de 5 sous-cohortes de sujets ayant débuté leur exposition aux benzodiazépines à des dates différentes (5, 8, 10, 13 et 15 ans après l'inclusion dans le programme PAQUID) de façon à mieux contrôler la dynamique de l'exposition et à évaluer son effet sur l'estimation du risque.

3.3.1.2. Définition de l'exposition et de l'*outcome*

Les données d'exposition aux benzodiazépines ont été collectées avec un questionnaire standardisé à chaque période de suivi et validées par la visualisation des conditionnements des médicaments consommés. Le diagnostic de démence incidente, *outcome* pour notre étude, était confirmé par un neurologiste.

3.3.2. Résultats

Dans la première approche, 95 nouveaux utilisateurs de benzodiazépines ont été comparés à 968 non-utilisateurs (âge moyen 78 ans). Au total, 253 cas incidents de démence ont été diagnostiqués au cours du suivi (30 parmi les utilisateurs et 223 parmi les non-utilisateurs). Dans une seconde approche, nous avons créé 4 cohortes de sujets ayant initié leur traitement postérieurement aux sujets de l'analyse principale afin de considérer 116 nouveaux utilisateurs et de les comparer à des non-utilisateurs vis-à-vis du risque de démence.
Dans la première approche, l'initiation de benzodiazépines était associée à une augmentation du risque de démence (HR ajusté 1,62 ; IC95 % 1,08-2,43) (Tableau 16). Dans la seconde, la méta-analyse des résultats des 5 cohortes (la cohorte principale et les 4 sous-cohortes) aboutissait à la même conclusion (HR 1,46 ; IC95 % 1,10-1,94) (Figure VI). Plusieurs arguments apparaissaient en défaveur d'un biais protopathique expliquant majoritairement les résultats : (i) l'augmentation du risque apparaissait 5 à 8 ans après l'initiation du traitement (courbes de Kaplan Meier (Figure V), (ii) la symptomatologie dépressive (prodrome potentiel de la maladie très associé à la prescription de benzodiazépines) n'était pas un facteur modificateur de l'effet (interaction benzodiazépine-dépression non significative, P=0,88) et l'ajustement sur ce paramètre ne modifiait pas l'association (Tableau 16), (iii) la force de l'association n'augmentait

pas lorsque le suivi disponible après le début de l'exposition diminuait (seconde approche, Figure VI).

3.4. Etude cas-témoins

3.4.1. Méthode

Une étude cas-témoins conduite dans PAQUID avait pour objectif de valider ces résultats par une méthode différente et complémentaire. Nous avons comparé 467 sujets atteints de démence à 1810 sujets qui ne l'étaient pas, vis-à-vis de leur exposition antérieure aux benzodiazépines catégorisée de la façon suivante: (i) initiation du traitement 5 ans ou plus avant la démence (exposition *a priori* la moins susceptible d'engendrer un biais protopathique), (ii) initiation du traitement moins de 5 ans avant la démence (exposition plus suspecte de biais protopathique), (iii) sujets non-exposés tout au long de leur suivi (référence).

3.4.2. Résultats

Comme dans les études prospectives, nous concluons (modèle de régression logistique conditionnelle ajusté sur les principaux facteurs de confusion décrits pour les études prospectives et mesurés 7-8 ans avant la date de diagnostic de la maladie) à une augmentation du risque de démence dans le groupe des sujets exposés aux benzodiazépines plus de 5 ans avant la démence (RC 1,56 ; IC95 % 1,23-1,98). L'augmentation, du même ordre de grandeur, n'était pas statistiquement significative chez les exposés plus récents (argument *a priori* en défaveur d'un biais protopathique). (Tableau 20).

3.5. Discussion et conclusion

La consommation de benzodiazépines était associée à une augmentation d'environ 50 à 60 % du risque de démence. Cette association était mise en évidence sur la base d'un long suivi (maximum 20 ans) et après avoir contrôlé les principaux facteurs potentiellement modificateurs ou confondants.

Malgré l'introduction d'une période de pré-inclusion de 5 ans ayant permis d'exclure les cas prévalents de démence et les consommateurs prévalents de benzodiazépines et malgré la prise en compte de certains prodromes ou facteurs de risque de la maladie fortement associés à la consommation de benzodiazépines, un biais protopathique ou de confusion résiduel ne pouvait

être exclu. De plus, le manque de certaines données (ex : dose) et la taille insuffisante des échantillons n'ont pas permis de considérer une relation dose-effet ou la nature des molécules (durée d'action) dans l'évaluation de la relation.
En revanche, ces études, conduites au sein d'une cohorte représentative des personnes âgées vivant en France, confirmaient les résultats d'études précédentes réalisées dans d'autres pays (Canada, Taïwan, Royaume-Uni).[5 6 8 9] L'extrapolation des résultats à une population plus jeune était par contre hasardeuse.

Ces trois études ont donné lieu à une publication dans le British Medical Journal en Septembre 2012[149] et une réactivité des agences de santé Française (messages d'information sur les sites, lettre aux prescripteurs, groupes de travail analysant la réalité du risque, voir Annexes 3).

4. Etude BENZODEM2 sur une base de données canadienne, la RAMQ (Partie IV)

4.1. Objectif

Nous avons réalisé une étude cas-témoins utilisant les données de la Régie de l'Assurance Maladie du Québec (RAMQ) afin (i) de valider les résultats des études réalisées dans PAQUID (programme BENZODEM, section 3) sur une population différente, (ii) de rechercher des critères de causalité (effet de la durée de traitement, de la nature des molécules comme la demi-vie d'élimination), non accessibles dans PAQUID.

4.2. Population

Une extraction aléatoire à partir des sujets de plus de 66 ans enregistrés sur la base de données de la RAMQ a été réalisée entre 2000 et 2009. Cette base regroupait des données de remboursement très nombreuses (médicaments, diagnostics médicaux etc.) concernant la quasi totalité des sujets de plus de 66 ans vivant au Québec. Nous avions de plus accès au doses et durées de traitement avec des effectifs rendant possible des analyses en sous-groupes. Enfin, la durée de suivi (10 ans), quoique un peu juste, semblait suffisante pour la recherche d'un lien entre consommation de benzodiazépines et démence.

4.3. Méthode

4.3.1. Cas et témoins

Dans cette étude cas-témoins, 1796 cas définis par un diagnostic de démence de type Alzheimer (ICD-9 : 331.0) et suivis depuis au moins 6 ans ont été appariés avec 7184 témoins (4 témoins par cas) de même sexe, âge et durée de suivi.

4.3.2. Exposition

Cas et témoins ont été comparés vis-à-vis-de l'exposition aux benzodiazépines initiée plus de 5 ans avant la date du diagnostic de la maladie. Cette période d'observation a été choisie car *a priori* moins susceptible d'être affectée par un biais protopathique que les expositions plus récentes. L'exposition aux benzodiazépines a d'abord été considérée globalement puis catégorisée selon (i) l'exposition cumulée exprimée en nombre de doses quotidiennes moyennes prescrites (*Prescribed Daily Doses* ou PDDs) classées en 3 catégories (1 à 90, 91 à 180, > 180) et (ii) selon la demi-vie d'élimination des molécules (courte, < 20h ou longues, ≥ 20h). Les non-utilisateurs de benzodiazépines durant la période d'observation servaient de groupe de référence. (Tableau 24).

4.3.3. Analyse statistique et ajustement

L'association entre consommation de benzodiazépines et risque de démence a été recherchée en utilisant une régression logistique conditionnelle prenant en considération différents facteurs de risque (en particulier cardiovasculaires) et comorbidités. L'influence éventuelle des potentiels prodromes (anxiété, dépression et insomnie) de la maladie a été prise en considération dans une analyse de sensibilité.

4.4. Résultats

L'exposition aux benzodiazépines « tous usages confondus » était associée à une augmentation significative du risque de maladie d'Alzheimer (RC ajusté 1,51 ; IC95 % 1,36-1,69). L'association n'était pas retrouvée chez les consommateurs de 3 mois ou moins. En revanche, le risque augmentait avec la densité d'exposition (1,32 (1,01-1,74) pour 91 à 180 PDDs, et 1,84 (1,62-2,08) pour plus de 180 PDDs) et pour les benzodiazépines à longue durée d'action (1,70 (1,46-

1,98) contre 1,43 (1,27-1,61) pour les molécules à courte durée d'action). La prise en compte de l'anxiété, la dépression ou l'insomnie présentées dans la littérature soit comme des prodromes (vérification de l'interaction avec les benzodiazépines dans l'estimation de l'association) soit comme des facteurs de risque (analyses de sensibilité avec ajustement supplémentaires sur ces paramètres, en l'absence d'interaction) de la maladie ne modifiait pas sensiblement les résultats (Tableau 26).

4.5. Discussion

4.5.1. Principales conclusions

Cette étude a permis de conclure à une augmentation du risque de démence de 43 à 51 % chez les utilisateurs de benzodiazépines, confirmant les résultats des travaux sur PAQUID (section 3). L'association apparaissait chez les utilisateurs de plus de trois mois cumulés, augmentait avec la durée d'utilisation et avec la demi-vie des molécules. Ces résultats ne semblaient pas majoritairement expliqués par un biais protopathique. En effet l'exposition était mesurée 5 ans et plus avant le diagnostic de la maladie (période moins critiquable vis-à-vis de ce biais). De plus la considération des prodromes de la maladie dans l'ajustement ne modifiait pas les résultats.

4.5.2. Limites

La recherche des cas étant basée sur les diagnostics enregistrés sur une base de données administratives sans accès direct au patient, des erreurs de classification ont pu se produire même si les diagnostics et leur codage étaient toujours réalisés par des médecins. Par ailleurs, la base de données de la RAMQ ne contenait pas les informations relatives au niveau d'étude, aux habitudes de consommation de tabac ou d'alcool, ces variables étant de possibles facteurs de confusion. Enfin, lors du codage, les symptômes neuropsychiatriques utilisés pour l'ajustement ont pu être sous-reportés dès lors qu'ils n'étaient pas considérés par les médecins comme des diagnostics principaux.

4.5.3. Reproductibilité des résultats

La population d'étude était représentative de la population du Québec rendant les résultats généralisables à l'ensemble des personnes âgées de cette province. En revanche, comme dans les études menées sur PAQUID, la généralisation des résultats à une population plus jeune serait critiquable.

4.6. Conclusion

Ces résultats confortent les conclusions du programme PAQUID. La mise en évidence d'une relation dose-effet marquée représente un argument supplémentaire et important en faveur d'une relation causale, au moins partielle. Comme la précédente, cette étude cas-témoins a fait l'objet d'une publication dans le British Medical Journal en septembre 2014,[179] assortie d'un éditorial.[209]

5. Analyses complémentaires (Partie V)

5.1. Contexte

Avant la publication des résultats de BENZODEM, des questions posées par des chercheurs nous ont conduit à réévaluer la relation entre consommation de benzodiazépines et la démence en prenant en considération le risque de mortalité compétitive (5.2). D'autres questions concernaient l'effet de la consommation d'autres psychotropes dans l'estimation de la relation entre benzodiazépines et démence. Nous avions considéré ce point dans des travaux préalables à la publication sans présenter leurs résultats du fait des limites de taille imposées par les éditeurs (5.3). Nous avons également cherché à vérifier des hypothèses concernant le mécanisme explicatif de la relation qui restait non élucidé (5.4). Nous avons enfin cherché à comprendre les paramètres expliquant l'usage très élevé de benzodiazépines chez les personnes âgées et son évolution dans le temps (5.5).

5.2. Benzodiazépines, démence & mortalité

5.2.1. Influence d'un potentiel risque compétitif démence-mortalité dans BENZODEM

Les événements compétitifs sont des « *outcomes* » survenant avec une fréquence notable dans les populations étudiées et pouvant influer sur l'estimation d'un autre risque. Dans les populations âgées, *a priori* suivies longtemps, la mort est typiquement un évènement compétitif potentiel vis-à-vis de l'« *outcome* » étudié. Nous avons donc conduit une nouvelle étude de cohorte comparant les 95 initiateurs de benzodiazépines de l'analyse principale de BENZODEM aux 968 non consommateurs vis-à-vis du risque de démence en utilisant une modélisation (modèle de Fine et Gray)[181] permettant de produire des estimations (Hazard Ratios, HR) corrigées en tenant compte de la mortalité comme événement en potentielle compétition avec la

démence dans l'estimation du risque lié à la consommation de benzodiazépines. L'estimation corrigée apparaissait similaire à l'estimation initiale (HR 1,55 ; IC95 % 1,04-2,32 *versus* HR 1,62 ; IC95 % 1,08-2,43). Ces résultats étant inattendus, nous nous sommes demandé si un différentiel de mortalité existait réellement entre consommateurs et non-consommateurs de benzodiazépines.

5.2.2. Etude de cohorte évaluant l'association entre consommation de benzodiazépines et mortalité

De nouvelles études de cohorte ont été menées dans PAQUID. Nous avons d'abord comparé des utilisateurs prévalents de benzodiazépines à l'inclusion dans PAQUID aux non-utilisateurs vis-à-vis du risque ultérieur de mortalité. La comparaison a été reproduite entre utilisateurs incidents de benzodiazépines à la première date de point suivant l'inclusion et non-consommateurs à cette date et antérieurement. Des analyses en sous-groupes ont permis de comparer les benzodiazépines à courte ou à longue demi-vie d'élimination. L'ajustement prenait en considération les principaux facteurs de confusion avec des analyses de sensibilité pour la dépression ou la consommation d'autres psychotropes (non benzodiazépiniques). Ces deux facteurs étaient en effet très liés à la consommation de benzodiazépines et de façon moins claire avec la démence (justifiant la vérification de leur influence sur l'association) avec pour conséquence un risque de colinéarité entre variables mesurant ces paramètres (justifiant le choix de ne pas les considérer dans l'analyse principale). Nous n'avons pas trouvé d'association (HR proches de 1) entre consommation de benzodiazépines et risque de mortalité quelle que soit la définition de l'exposition (incidente ou prévalence, molécules de longue ou de courte durée d'élimination) (Tableau 31 pour les utilisateurs prévalents et Tableau 32 pour les utilisateurs incidents). Ces résultats expliquaient l'absence de modification sensible des résultats dans le modèle de mortalité compétitive.

5.2.3. Simulation de l'évolution de la relation benzodiazépines-démence sous différentes hypothèses de mortalité différentielle entre les groupes comparés

Nous nous sommes ensuite demandé comment évoluerait l'estimation de la relation entre benzodiazépines et démence évaluée dans l'analyse prospective principale de BENZODEM (*i.e.* HR 1,62 ; IC95 % 1,08-2,43; section 3) si un risque de mortalité différentielle entre groupes apparaissait. En simulant des délais de survenue de la mort raccourcis de 20 et 50 % chez les exposés aux benzodiazépines décédés au cours du suivi, les HR ajustés prenant en considération la mortalité compétitive devenaient respectivement 1,72 (1,17-2,52), et 2,08 (1,42-3,04). En

faisant cette même simulation dans le groupe des non-utilisateurs, les HR ajustés devenaient respectivement 1,36 (0,93-2,00), et 1,13 (0,77-1,66). (Tableau 33).

5.2.4. Conclusion

La prise en compte de la mortalité en tant qu'évènement potentiellement compétitif ne changeait pas les estimations du fait qu'il n'existait pas de mortalité différentielle entre les groupes comparés. Les simulations considérant différentes hypothèses de mortalité différentielle entre groupes comparés montrent l'importance de prendre en considération les événements pouvant avoir une influence sur la durée de suivi. En particulier, la parfaite comparabilité des groupes vis-à-vis du risque de mortalité devrait être systématiquement vérifiée dans les études conduites au sein de populations âgées. Les abstracts des articles relatifs à ces études et en cours de soumission, sont disponibles en Annexes 1.

5.3. Autres psychotropes

5.3.1. Contexte

D'autres questions nous ont été posées (i) quant à l'influence des autres psychotropes (*i.e.* antidépresseurs, antipsychotiques, thymorégulateurs et autres) sur l'estimation de la relation entre benzodiazépines et risque de démence, (ii) quant à l'effet propre des autres psychotropes ou à leur action synergique à celle des benzodiazépines sur le risque de démence.

5.3.2. La relation benzodiazépines-démence est-elle modifiée par la consommation d'autres psychotropes ?

5.3.2.1. Analyses réalisées dans PAQUID

Nous avons utilisé l'échantillon et les groupes de comparaison décrits dans l'analyse principale BENZODEM (section 3) afin de rechercher une interaction entre consommation incidente de benzodiazépines et consommation d'autres psychotropes (définie par l'utilisation passée ou en cours d'autres psychotropes à la date de référence de l'étude (*i.e.* 5 ans après l'inclusion dans PAQUID, T_5). La vérification de l'absence d'interaction significative était le préalable à une analyse de sensibilité considérant un ajustement complémentaire sur la consommation d'autres psychotropes. Parmi les 1063 sujets inclus, 119 (11,2 %) avaient déclaré utiliser d'autres

psychotropes à la date de référence ou avant cette date (31,6 % parmi les nouveaux utilisateurs de benzodiazépines et 9,2 % parmi les non-utilisateurs) (Tableau 34). La consommation « en cours » ou passée d'autres psychotropes ne modifiait pas significativement l'association entre consommation de benzodiazépines et la démence (interaction non significative, P=0,88). L'ajustement complémentaire sur ce paramètre ne modifiait pas le sens de l'estimation entre nouvelle consommation de benzodiazépines et démence (Hazard Ratio 1,54 ; IC95 % 1,02-2,33 *versus* 1,62 (1,08-2,43)) (Tableau 35).

En revanche, il n'était pas possible d'évaluer l'effet de chaque famille de psychotropes sur le risque de démence indépendamment des benzodiazépines du fait des faibles effectifs disponibles dans PAQUID (Tableau 34).

5.3.2.2. Analyses réalisées avec les données de remboursement de la RAMQ

L'étude cas-témoins conduite en utilisant la base de données de la RAMQ (section 4) permettait, du fait d'un échantillon plus important, d'évaluer l'effet modificateur ou la confusion induite par les antidépresseurs sur l'estimation entre consommation de benzodiazépines et le risque de maladie d'Alzheimer. Nous nous sommes concentrés sur cette famille de psychotropes car :

- les antidépresseurs sont souvent prescrits avec les benzodiazépines,
- ils sont les psychotropes les plus fréquemment prescrits après les benzodiazépines,
- ils sont un marqueur de dépression, elle-même prodrome ou/et facteur de risque de la maladie ; l'évaluation du rôle des antidépresseurs pouvait donc contribuer à mieux prendre en compte le risque de biais protopathique,
- les effectifs d'utilisateurs d'autres psychotropes étaient trop faibles pour envisager des analyses spécifiques et des conclusions stables.

Comme dans PAQUID, nous avons recherché une interaction entre consommation d'antidépresseurs et de benzodiazépines dans l'association avec le risque de maladie d'Alzheimer (l'absence d'interaction significative autorisant l'introduction de la variable « antidépresseurs » dans le modèle d'ajustement). L'usage d'antidépresseurs a été mesuré durant la même période d'observation que pour les benzodiazépines (*i.e.* 5 ans ou plus avant le diagnostic de la maladie). Parmi les 8980 sujets inclus dans l'étude RAMQ (section 4), 1610 (17,9 % ; 24,3 % des cas et 16,3 % des témoins) avaient reçu au moins un remboursement d'antidépresseur durant la période observée. Leur usage ne modifiait pas l'association entre benzodiazépines et risque de démence (interaction non significative, P=0,74) qui demeurait significative après un ajustement complémentaire sur les antidépresseurs (Rapport de Cotes, RC 1,35 ; IC95 % 1,20-1,55 *versus* 1,43 (1,28-1,60)) (Tableau 36).

5.3.3. Evaluation de la relation entre autres psychotropes et démence (synergie d'effet avec les benzodiazépines, effet indépendant)

5.3.3.1. Analyses réalisées dans PAQUID

En utilisant les mêmes échantillons que ceux de l'étude cas-témoins BENZODEM (section 3), nous avons d'abord considéré plusieurs catégories d'usage de benzodiazépines ou d'autres psychotropes pendant toute la période précédant le diagnostic de la démence : (i) exposés au moins une fois aux benzodiazépines mais jamais à d'autres psychotropes, (ii) exposés aux benzodiazépines et à d'autres psychotropes de façon concomitante ou non, (iii) exposés à d'autres psychotropes mais pas aux benzodiazépines, (iv) jamais exposés aux benzodiazépines ni à d'autres psychotropes (groupe de référence). Dans un second temps, huit catégories d'exposition aux benzodiazépines et aux autres psychotropes ont été définies en tenant compte de la période d'exposition : initiation récente (5 ans ou moins avant le diagnostic de la maladie) et initiation passée (plus de 5 ans avant le diagnostic de la maladie) (Tableau 38).

Cette seconde définition avait pour but d'évaluer l'influence du biais protopathique sur les estimations (les expositions récentes étant plus suspectes de ce point de vue). 96 cas (20,6 %) et 260 témoins (14,4 %) avaient utilisés à la fois des benzodiazépines et d'autres psychotropes durant la période observée ; 23 cas (4,9 %) et 65 témoins (3,6 %) uniquement d'autres psychotropes. Parmi les 444 utilisateurs d'autres psychotropes, 356 (80,2 %) avaient aussi utilisé des benzodiazépines (dans la même proportion pour les cas et les témoins). Parmi les 892 utilisateurs de benzodiazépines, 39.9 % avaient aussi utilisé d'autres psychotropes (45.7 % des cas et 38.1 % des témoins). Avoir utilisé à la fois des benzodiazépines et d'autres psychotropes était associé à une augmentation significative de 80% du risque de démence. Ce risque était plus élevé que pour l'usage de benzodiazépines ou d'autres psychotropes seuls (Tableau 37). En considérant la période d'initiation des traitements (récente ou passée), l'augmentation du risque de démence chez les utilisateurs de benzodiazépines et d'autres psychotropes était expliquée d'avantage par l'initiation passée de ces traitements (Rapport de Cotes ajusté RC 1,91 ; IC95 % 1,34-2,71) que par l'initiation récente de l'un de ces traitements. Toute conclusion quant à l'effet des autres psychotropes (non associés aux benzodiazépines) était impossible du fait des faibles échantillons disponibles pour les analyses (Tableau 38).

De façon intéressante, on notait une augmentation du risque de démence à la limite de la significativité statistique chez les sujets ayant initié un traitement par benzodiazépines seules plus de 5 ans avant le diagnostic de la maladie.

5.3.3.2. Analyses réalisées avec les données de remboursement de la RAMQ

Nous avons utilisé les mêmes groupes de comparaison que pour l'étude cas-témoins BENZODEM2 (section 4) afin d'évaluer : (i) l'effet synergique de l'association entre consommation de benzodiazépines et d'antidépresseurs, (ii) l'effet propre des antidépresseurs sur le risque de maladie d'Alzheimer. L'exposition à ces médicaments a été recherchée durant les 5 à 10 années précédant le diagnostic de maladie d'Alzheimer. Comme pour les données PAQUID, l'exposition a été catégorisée en considérant (i) l'usage de benzodiazépines seules, (ii) l'usage de benzodiazépines et d'antidépresseurs de façon concomitante ou non, (iii) l'usage d'antidépresseurs seuls, (iv) la non-utilisation de benzodiazépines et d'antidépresseurs (groupe de référence). Cas et témoins appariés ont été comparés vis-à-vis de l'exposition aux benzodiazépines et aux antidépresseurs telle que précédemment définie. Les modèles de régression logistique permettant d'estimer l'association entre consommation de benzodiazépines et le risque de démence ont été ajustés sur les facteurs de confusion décrits dans l'étude BENZODEM2 (section 4). Parmi les 8980 sujets inclus, 1157 (12,9 %) avaient utilisé des benzodiazépines et des antidépresseurs (18,4 % des cas et 11,5 % des témoins). La plupart des consommateurs d'antidépresseurs (71,9 %, n=1610) avaient également utilisé des benzodiazépines durant la période observée (75,7 % des cas et 70,4 % des témoins). Le contraire était retrouvé pour les utilisateurs de benzodiazépines (n=3767) chez lesquels l'usage d'antidépresseurs était moins fréquent (30,7 %; 37,0 % des cas et 28,8 % des témoins) (Tableau 39).

Un effet significatif indépendant était retrouvé à la fois pour les utilisateurs de benzodiazépines et d'antidépresseurs seuls comparés aux non-utilisateurs de ces deux classes (augmentation du risque d'environ 40 % et 50 %, respectivement). Le risque de maladie d'Alzheimer était plus élevé en cas d'association de benzodiazépines et d'antidépresseurs (Rapport de Cotes ajusté RC 2,04 ; IC95 % 1,61-2,23). (Tableau 39).

5.3.4. Discussion

5.3.4.1. L'association benzodiazépines-démence est-elle modifiée pas l'usage d'autres psychotropes?

L'association benzodiazépines et démence demeure significative indépendamment de l'utilisation d'autres psychotropes ce qui est un argument en faveur d'un effet propre des benzodiazépines.

5.3.4.2. Synergie d'effet et effet propre des autres psychotropes

L'usage de benzodiazépines et d'autres psychotropes (PAQUID), ou d'antidépresseurs (RAMQ) au cours des 5 à 10 ans précédant la démence était associé à une augmentation du risque plus forte que l'utilisation seule de benzodiazépines ou d'autres psychotropes (PAQUID) ou d'antidépresseurs (RAMQ). L'interprétation de ce résultat est complexe : (i) synergie d'effet, (ii) l'association à un psychotrope correspondait à l'utilisation de doses plus élevées ou à des durées plus longues de benzodiazépines, (iii) l'association identifiait des malades présentant des formes plus sévères d'anxiété, dépression ou trouble du sommeil, facteurs de risque, voire prodromes d'une démence future, (iv) autres explications.
Le fait que les autres psychotropes, particulièrement les antidépresseurs soient, en eux-mêmes, associés à un risque augmenté de démence est également complexe à interpréter.
La recherche d'un effet propre des autres psychotropes ou d'une possible synergie d'effet avec les benzodiazépines nécessiterait la mise en place de protocoles spécifiques et l'accès à des effectifs importants pour pouvoir isoler chaque famille de psychotropes dont les indications, les modes d'utilisation, les mécanismes d'action et les hypothèses biologiques sous-tendant leur possible effet sur la cognition sont différents.

5.4. Mécanismes explicatifs de l'association benzodiazépines-démence

5.4.1. Contexte, objectif

Le mécanisme biologique à l'origine de la relation entre benzodiazépines et démence reste inexpliqué alors qu'il serait majeur de statuer sur le caractère causal ou non de cette association du fait de son impact potentiellement très élevé. Certaines études ont montré un déclin cognitif accéléré chez les utilisateurs de benzodiazépines[184 186] alors que d'autres non.[124 176 177] Néanmoins aucune d'elles ne considérait une potentielle relation entre consommation de benzodiazépines et démence. En effet, le déclin cognitif propre à la démence pourrait avoir conduit à surestimer le rôle intrinsèque des benzodiazépines. Une nouvelle étude a donc été conduite dans le but d'évaluer l'effet de l'initiation des benzodiazépines sur le risque d'altération cognitive à long terme chez des sujets âgés initialement non atteints de démence et considérant la possibilité d'apparition de cette maladie au cours du suivi et son influence sur les estimations.

5.4.2. Méthodes

Une étude de cohorte a été menée au sein du programme PAQUID incluant les sujets consommateurs de benzodiazépines à la date d'inclusion dans la cohorte ainsi que les sujets non-consommateurs à cette date et à la date de suivi suivante (T_3, date de référence choisie pour l'étude). L'exposition aux benzodiazépines était définie par une consommation initiée à T_3. Le groupe de référence (non-consommateurs) était constitué de sujets n'ayant pas déclaré consommer de benzodiazépines à T_3 ni avant cette date. Les fonctions cognitives ont été évaluées à chaque suivi (*i.e.* tous les 2-3 ans depuis la date de référence) à partir des scores obtenus au Mini Mental State Examination (MMSE)[152] évaluant le fonctionnement cognitif global, au Set Test d'Isaac (IST)[154] évaluant la fluence et la mémoire verbales et au test de Benton (BVRT)[153] évaluant les fonction visuo-spatiales et la mémoire visuelle. L'association entre consommation de benzodiazépines et l'évolution des performances cognitives a été étudiée en utilisant des modèles non linéaires à effets mixtes considérant en tant que variable dépendante un processus latent. Ces modèles ont été ajustés sur des variables constantes (sexe, âge, niveau d'études) et sur des variables dépendantes du temps (consommation de vin, statut marital, utilisation d'autres médicaments psychotropes, utilisation de médicaments à visée cardiovasculaire). Une analyse de sensibilité a consisté à exclure de l'échantillon les sujets avec un diagnostic de démence au cours du suivi de façon à éliminer l'influence potentielle de cette maladie sur l'évaluation du déclin cognitif.

5.4.3. Résultats

Après ajustement, on ne notait pas d'effet significatif de l'initiation d'un traitement par benzodiazépines sur le déclin cognitif quel que soit le test utilisé pour l'évaluation (MMSE : P=0,19 ; IST : P=0,08 ; BVRT : P=0,85). L'exclusion des sujets atteints de démence au cours du suivi ne modifiait pas le sens de ces résultats. (Tableau 41).

5.4.4. Discussion

Cette étude ne met pas en évidence un effet propre des benzodiazépines nouvellement initiées sur les performances cognitives ni sur leur évolution dans le temps quelle que soit la période considérée (court ou long terme depuis l'initiation du traitement), et ce malgré la prise en considération du risque concomitant de démence. Ces résultats pourraient d'abord paraître contredire ceux montrant un lien entre les benzodiazépines et démence. Ce n'est pas le cas. Tout d'abord, toute altération cognitive ne signe pas le développement d'une démence. Ensuite, cette

étude permet d'écarter certaines objections faites à l'encontre des travaux montrant un lien entre ces médicaments et la démence notamment quant à la possibilité d'un « biais protopathique ». Une objection formulée à l'encontre des études antérieures était que certaines démences n'étaient pas de vraies démences mais seulement des altérations cognitives induites par les benzodiazépines. Cette étude ne va pas dans ce sens puisqu'en cas d'altération cognitive préexistante celle-ci n'était pas aggravée avec la prise de benzodiazépines. L'association benzodiazépines-démence ne semble donc pas liée à un déclin cognitif ni à un effet « toxique » direct des benzodiazépines. Plusieurs hypothèses seront émises dans la discussion générale de ce travail (section 6). L'abstract d'un article relatif à cette étude et en préparation avant soumission, est disponible en Annexes 1.

5.5. Objectifs descriptifs

5.5.1. Facteurs associés à la consommation de psychotropes en population agricole

5.5.1.1. Contexte et objectifs

Les spécificités de la vie en milieu rural (pénurie de médecins, isolement, bas niveau d'études, faibles revenus, activité physique importante, meilleure alimentation et soutien familial etc.) pourraient être à l'origine de différences concernant l'usage de psychotropes par rapport à ce qui est connu en population générale. Notre objectif était d'évaluer la prévalence et les caractéristiques du recours aux médicaments psychotropes, jusqu'alors peu documentées, en différenciant les deux principales familles (benzodiazépines et antidépresseurs) dans une population de sujets vivant en milieu rural.

5.5.1.2. Population, schéma d'étude

Nous avons mené une étude transversale au sein de la cohorte AMI, étude épidémiologique sur le vieillissement dont l'originalité était de s'intéresser spécifiquement à l'état de santé de retraités agricoles vivant en milieu rural. Le programme a permis d'inclure 1002 sujets de 65 ans et plus, vivant en Gironde rurale et retraités du régime agricole après au moins 20 ans d'activité et sélectionnés de façon aléatoire entre septembre 2007 et décembre 2008 parmi les assurés à la Mutualité Sociale Agricole (MSA). Le programme inclut des visites à domicile tous les 2 ans avec entretiens téléphoniques entre ces visites. De nombreuses données sont recueillies concernant les habitudes de vie, l'état de santé des patients, la cognition, la dépendance et une recherche systématique des signes et cas de démence. Les données de

sécurité sociale de la MSA (consommations médicamenteuses, remboursements de soins médicaux et paramédicaux etc.) sont accessibles. Les caractéristiques de cette cohorte ont été précédemment décrites.[194]

5.5.1.3. Principales conclusions

Nous avons mis en évidence une prévalence d'usage de psychotropes moins élevée que celle mesurée en population générale (ex : PAQUID). Cette différence était moins marquée pour les hommes que pour les femmes, et plus marquée quel que soit le sexe, pour les benzodiazépines. Une régression logistique multivariée a mis en évidence des facteurs associés à la consommation de psychotropes non spécifiques à la population rurale : sexe féminin, âge plus avancé (pour les benzodiazépines) et moins avancé pour les antidépresseurs, mauvaise satisfaction de la vie, polypathologie, vivre en institution et consommer d'autres psychotropes. Il existait cependant certaines caractéristiques plus spécifiques à cette population rurale : contrairement à PAQUID, la symptomatologie dépressive était davantage associée à la consommation d'antidépresseurs qu'à celle d'anxiolytiques, l'anxiété était associée à la consommation d'antidépresseurs mais pas à celle d'anxiolytiques, un plus haut niveau de dépendance était associé à une plus grande consommation de psychotropes (plutôt des antidépresseurs) et à une moins grande consommation de benzodiazépines et, enfin, des troubles cognitifs sans démence étaient associés à la prescription d'antidépresseurs mais pas à celle de benzodiazépines. L'abstract d'un article relatif à cette étude et en préparation, est disponible en Annexes 1.

5.5.2. Evolution des facteurs associés à la consommation de psychotropes

5.5.2.1. Contexte et objectifs

Notre objectif était d'évaluer l'évolution de la prévalence d'usage et des facteurs associés à la consommation de psychotropes chez des personnes âgées en considérant les principales familles de psychotropes (benzodiazépines et antidépresseurs).

5.5.2.2. Population, schéma d'étude

Nous avons effectué deux études descriptives dans la cohorte PAQUID décrite précédemment.[147] Les populations sources de ces études étaient constituées par deux générations de sujets ayant eu 75 ans et plus entre 1988 et 1998 pour la première et entre 2001 et 2008 pour la seconde.

5.5.2.3. Principales conclusions

La prévalence d'usage de psychotropes était élevée, environ 50% et ne variait pas entre les deux périodes. La consommation d'antidépresseurs semblait avoir augmenté ce qui pourrait être en lien avec la publication, dans l'intervalle, des recommandations concernant leur prescription chez les personnes âgées. Par contre, la prévalence d'usage des benzodiazépines restait élevée et stable malgré les recommandations incitant à limiter leur utilisation. L'abstract d'un article relatif à ces études et en préparation, est disponible en Annexes 1.

6. Discussion générale (Partie VI)

Nous avons mis en évidence dans deux études de cohorte et deux études cas-témoins un risque de démence chez les consommateurs de benzodiazépines. L'étude canadienne (BENZODEM2, section 4) souligne que cet excès de risque est associé à un usage supérieur à 3 mois (hors règlementation). Nous nous sommes posé plusieurs questions à l'issue de ce travail :

- La causalité du lien entre benzodiazépines et la démence est-t-elle probable ? (Cf. 6.1)
- Quelles populations ou quels groupes d'utilisateurs seraient à risque ? (Cf. 6.2)
- Quelles sont les implications pour la santé publique et la pratique clinique ? (Cf. 6.3)
- Quelles autres recherches serait-il intéressant de mener sur le sujet ? (Cf. 6.4)

6.1. La causalité du lien entre benzodiazépines et la démence est-t-elle probable ?

Dans un article rédigé à la demande de la revue Expert Opinion on Drug Safety[199] et publié en Février 2015, nous répondons que la causalité de la relation n'est pas prouvée mais que différents arguments permettaient de considérer qu'elle est au moins possible. En effet, en faisant référence au travail de Bradford Hill,[201] cinq des neuf critères de causalité proposés pourraient être plus ou moins remplis :

- *Concordance des résultats.* L'association entre consommation de benzodiazépines et la démence était statistiquement significative et de même ampleur dans sept études[5 7-9 149 179] menées par différentes équipes de recherche, en utilisant des sources de données et des approches distinctes.

- *Temporalité de l'association.* Ce critère fondamental de causalité implique que le début de l'exposition précède l'effet observé. En considérant le diagnostic clinique de la démence, ce critère était rempli par toutes les études. Néanmoins, compte tenu de la longue période infra-clinique de la maladie, sa véritable date de début ne peut être établie précisément. Cette limite était partiellement contournée par les études rapportant une association avec les traitements débutés plusieurs années avant le diagnostic.[7-9 149 179]

- *L'existence d'une relation dose-effet* est un autre argument majeur de causalité. Une relation entre la densité de l'exposition et la magnitude de l'association a été recherchée dans quatre études,[5 8 9 179] absente dans d'une d'elles,[9] mais présente dans les autres et de façon marquée dans l'une d'elles.[179] Bien que convaincant, cet argument est discutable puisque l'usage à long terme ou de fortes doses de benzodiazépines pourraient aussi correspondre aux formes les plus sévères d'anxiété, d'insomnie ou de dépression qui sont des prodromes ou des facteurs de risque possibles de la maladie.

- *Plausibilité et cohérence de l'association*. Aucun mécanisme physiopathologique ne peut expliquer avec certitude l'effet retrouvé entre consommation de benzodiazépines et risque augmenté de démence. L'association ne semble pas résulter d'une augmentation du risque de déclin cognitif à long terme (cf. section 5). En revanche, le fait que les benzodiazépines puissent amputer la réserve cognitive[51] constitue une hypothèse biologique plausible : De nombreuses études suggèrent que la stimulation intellectuelle permet de retarder l'apparition d'une démence, probablement en favorisant une certaine plasticité cérébrale. Il est possible que les benzodiazépines aient l'effet inverse : leur usage prolongé pourrait diminuer la mobilisation de cette réserve, accélérant le début de la maladie. Il est néanmoins possible que les benzodiazépines n'aient pas d'effet direct sur le risque de démence mais représentent plutôt (en tant que principal traitement de l'anxiété), un marqueur, les personnes ayant des problèmes d'anxiété récurrents étant ensuite à plus haut risque de démence. Ceci serait tout de même intéressant car permettant d'identifier précocement des personnes ayant un risque augmenté. Il n'est pas exclu que l'association entre benzodiazépines et démence combine ces deux précédentes hypothèses (effet sur la plasticité cérébrale et marqueur précoce d'un risque plus grand de démence).

Sur la base de ces arguments, il parait sensé de considérer qu'un rôle causal des benzodiazépines est au moins possible même si d'autres critères de causalité tels que la force

élevée de l'association, la spécificité, les preuves expérimentales ou l'analogie ne sont pas remplis.

6.2. Quelles populations ou quels groupes d'utilisateurs seraient à risque ?

La plupart des études, dont les nôtres, ont été conduites chez les personnes âgées, même si l'inclusion commençait à 45 ans dans deux études.[5 8] Ces personnes sont incontestablement plus vulnérables aux effets secondaires neurocognitifs et les benzodiazépines pourraient d'autant plus altérer leur capacité de réserve cognitive et réduire leur possibilité de compensation face aux lésions débutantes de la maladie. Au regard des connaissances actuelles, aucune conclusion ne peut être émise sur un possible risque en excès lié à une exposition chez des personnes jeunes.

D'après plusieurs études, l'effet délétère des benzodiazépines ne serait à craindre que chez les utilisateurs à long terme. En effet, notre étude Canadienne[179] conclut à une absence d'association chez les utilisateurs de moins de 3 mois. Une autre concluait à une régression du risque à l'arrêt du traitement chez les utilisateurs de moins de trois mois mais pas chez les utilisateurs à plus long terme.[8]

Aucune conclusion ne peut être tirée quant à une différence de toxicité entre les benzodiazépines et les molécules pharmacologiquement apparentées (ex : zolpidem, zopiclone et zaleplon) généralement prises en compte de façon globale pour définir l'exposition aux « benzodiazépines ». Néanmoins, les benzodiazépines apparentées incluant majoritairement des molécules à courte demi-vie d'élimination, il est sensé de considérer que leur risque serait du même ordre de grandeur que celui des benzodiazépines à demi-vie courte moins élevé que celui des molécules à demi-vie longue.[179]

6.3. Quelles implications pour la santé publique et la pratique clinique ?

Conclure que les benzodiazépines (au moins leur utilisation à long terme) pourraient augmenter de 1,5 à 2 fois le risque de démence aurait des conséquences dramatiques pour la santé publique et l'économie, si la relation s'avérait être causale. La consommation de ces médicaments est fréquente chez les sujets âgés,[111 206-208] et le plus souvent chronique contrairement aux recommandations de bon usage. Bien que les benzodiazépines restent très utiles pour traiter l'anxiété et l'insomnie, leurs effets délétères sur la cognition (bien établis à court terme, avec un certain nombre d'éléments faisant craindre un risque de démence à long terme) ainsi que le principe de précaution suggèrent de restreindre l'utilisation de ces médicaments à des traitements de courte durée et pleinement justifiés. Il n'y a actuellement aucune évidence d'un

risque augmenté de démence pour des utilisations conformes à la règlementation (n'excédant pas 1 mois pour les hypnotiques et 3 mois pour les anxiolytiques). En conséquence, il paraît crucial d'évaluer précautionneusement le rapport bénéfice/risque lors de l'initiation et du renouvellement du traitement. L'arrêt des traitements à long terme ne doit toutefois jamais être brutal du fait des risques liés au sevrage.

6.4. Quelles autres recherches serait-il intéressant de mener sur le sujet ?

De nouvelles études seraient nécessaires afin d'évaluer le risque des traitements initiés chez des personnes jeunes. Ces études nécessiteraient cependant de très longues durées de suivi (au moins 30 ans) avec un recueil régulier d'informations valides sur l'exposition médicamenteuse, la cognition, les prodromes et facteurs de risque de démence. Ce type de données est en pratique très difficile à obtenir mais permettrait de rechercher également le rôle de l'anxiété, l'insomnie, la dépression (dont la nature de la relation avec la démence est inconnue) en milieu de vie. Des modèles animaux ou cellulaires pourraient également aider à identifier les mécanismes neurobiologiques pouvant associer les benzodiazépines à la démence. Cette dernière approche si elle était concluante ajouterait un argument majeur de causalité.

7. Conclusion générale

Nos travaux de recherche incluant les études réalisées dans le cadre des programmes BENZODEM et BENZODEM2 ainsi que plusieurs études complémentaires renforcent la suspicion d'un risque augmenté de démence associé à la consommation de benzodiazépines. Malgré notre approche graduelle de la question, ayant consisté en des études et des analyses spécifiques conceptualisées à chaque étape, le caractère causal de l'association reste non démontré. Néanmoins, un certain nombre d'arguments plaident en faveur d'une association semblant non expliquée ou non majoritairement expliquée par un biais résiduel ou de causalité inversée : plausibilité biologique de l'association, relation dose-effet, persistance de l'effet malgré la prise en compte des principaux facteurs de risque, des prodrome de la maladie et des traitements associés, excès de risque retardé par rapport à l'initiation du traitement, concordance avec les résultats de travaux ayant utilisé des approches et des populations différentes.

A ce stade, même si la nature causale de l'association est loin d'être établie, elle pourrait être considérée comme au moins possible. Il est essentiel de ne pas perdre de vue que l'incidence de la démence et la consommation de benzodiazépines étant toutes deux élevées, particulièrement chez les personnes âgées, une augmentation, même modérée, du risque de démence aurait des

conséquences catastrophiques en terme de nombre de cas en excès et aurait un impact majeur de santé publique. Un résultat primordial de l'étude BENZODEM2 est que les traitements conformes aux durées recommandées ne seraient pas à risque.

Les éléments semblent d'ores et déjà suffisants pour appliquer le principe de précaution : les indications non justifiées et l'usage prolongé des benzodiazépines devraient être proscrits. Considérant la fréquence anormalement élevée de la prescription chez les personnes âgées, dans la plupart des pays industrialisés, ainsi que les autres effets secondaires de cette classe de médicaments (chutes, fractures, etc.), nos résultats devraient encourager la prise de mesures incitant à respecter les règles de prescription des benzodiazépines.

De nouvelles études seraient nécessaires pour identifier le mécanisme de l'association ainsi que pour mieux comprendre le rôle des symptômes associés comme l'anxiété, les troubles du sommeil et la dépression et, enfin, pour évaluer la plausibilité du risque chez les utilisateurs plus jeunes. Ces considérations sont cependant en dehors des objectifs de cette thèse.

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ANNEXES

Annexes 1: Publications

1. Article published

- BENZODEM

Billioti de Gage S, Begaud B, Bazin F, Verdoux H, Dartigues JF, Peres K, et al. Benzodiazepine use and risk of dementia: prospective population based study. *BMJ* 2012;345:e6231.

- BENZODEM2

Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ* 2014;349:g5205.

- Literature review about the relationship between benzodiazepines and dementia

Billioti de Gage S, Pariente A, Begaud B. Is there really a link between benzodiazepine use and the risk of dementia? *Expert Opin Drug Saf* 2015:1-15.

2. Articles in submission process (cf. Abstracts)

- Abstract #1: Competing risks: why should we care in pharmacoepidemiology research?

- Abstract #2: Global mortality associated with benzodiazepine use.

- Abstract #3: Benzodiazepine new use and long-term cognitive decline in the elderly: a prospective cohort study.

- Abstract #4: Characteristics associated with psychotropic use in a French cohort of elderly farmers.

- Abstract #5: Temporal trends of the characteristics associated with psychotropic use in a French cohort of elderly persons.

Abstract #1: Competing risks: why should we care in pharmacoepidemiology research?

A. Pariente *MD-PhD*[1 2 3], S. Billioti de Gage *PharmD-PhD candidate*[1 2], J. Bezin *PharmD-PhD candidate*[1 2 3], F. Salvo *MD-PhD*[1 2 3], M. André *MSc*[1 2], B. Bégaud *MD-PhD*[1 2 3]

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Objective: To illustrate how competing risks can modify association quantifications in pharmacoepidemiology studies.

Design, Settings, and Participants: The first 20 years of follow-up of the PAQUID study on ageing were used to assess the risk of incident dementia associated with the initiation of benzodiazepines in subjects aged 70 and over.[149] The analyses used mutivariable Cox proportional hazard models. Before the manuscript was accepted, referees pointed out a possible competing risk of death in the elderly as an influence on the study results. As this risk is little considered in pharmacoepidemiology, we decided to perform simulations to illustrate the potential effect of competing risks on association estimates. A competing event is an outcome that occurs frequently in the studied population and may interfere with other risk evaluations. Death is traditionally considered as such in elderly populations. To study the modifications that can be observed for the association between benzodiazepine initiation and the risk of dementia, we simulated variations in the Hazard Ratio of death among benzodiazepine initiators and non-initiators included in our study, while the incidence of dementia was unmodified. Analyses were performed using Cox proportional Hazard models similar to those used in the initial study.

Results: In the initial publication, 30 cases of dementia were confirmed in the 95 benzodiazepine initiators, and 223 in the 968 non-initiators. The Hazard Ratio (HR) for the association estimated initially through Cox models was 1.62 (1.08 to 2.43); HR for death was 1.12 (0.82 to 1.50) indicating no potentiality of competing bias. When shortening the death onset delay by 20% and 50% in benzodiazepine initiators, the Cox estimated HR for the association was 1.72 (1.17-2.52), and 2.08 (1.42-3.04), respectively. Conversely, when shortening the death onset delay by 20% and 50% in benzodiazepine non-users, these HRs were 1.36 (0.93-2.00), and 1.13 (0.77-1.66), respectively.

Conclusion: When studying a risk in a population in which other events are likely to frequently occur and to impact follow-up duration, competing risks should be considered when estimating associations. In particular, the risk of death should be systematically checked in pharmacoepidemiology studies conducted on the elderly.

Key words: competing risks, mortality, pharmacoepidemiology, benzodiazepines, dementia

Abstract #2: Global mortality associated with benzodiazepine use

S. Billioti de Gage *PharmD*-PhD[1 2], B. Bégaud *MD-PhD*[1 2 3]

[1]Université de Bordeaux, Bordeaux, France; [2]INSERM, U657, Bordeaux, France; [3]CHU de Bordeaux, Bordeaux, France.

Objective: To assess the putative long-term excess risk of mortality in benzodiazepine users.

Design, Settings, and Participants: A prospective study was conducted in a cohort of elderly people aged 65 years and over, identified among participants in the prospective PAQUID programme. The first 20 years of follow-up of this programme were available for analysis. We first compared prevalent users of benzodiazepines to non-users at inclusion in the PAQUID programme regarding subsequent risk of mortality. Next, we made the same comparison between incident users of benzodiazepines and never users at the first time point (*i.e.* 3 years after inclusion, T_3). Subgroup analyses of benzodiazepine users were conducted in order to evaluate a putative effect of the molecule elimination half-life (long, *i.e.* ≥20 h or short). A Cox model adjusted on the main putative confounders measured at inclusion (T_0) in the PAQUID programme (*i.e.* age, gender, education level, singleness, several variables associated with cardiovascular risk, MMSE, perceived health, depressive disorders and the use of other psychotropics) was used to estimate the Hazard Ratios (HRs) for mortality between groups.

Results: During the 20-year follow-up, 1002 (82.7%) deaths were confirmed among subjects using benzodiazepines at inclusion (prevalent users) and 2036 (79.4%) among non-users at this date. During the 17-year follow-up, 182 (82.4%) deaths were confirmed among incident users of benzodiazepines at T_3 and 1087 (74.8%) among non-users at this date. Prevalent use of benzodiazepines was not associated with an excess risk of mortality (HR 0.99, 95%CI 0.91 to 1.07) in the model adjusted on the above-mentioned covariates. The same conclusion was true for incident use of benzodiazepines (HR 1.12, 95%CI 0.94 to 1.32) in the model adjusted on the same covariates. These conclusions remained unchanged when considering the use of long- or short-acting molecules.

Conclusion: We found no association between benzodiazepine use and an increased risk of mortality, whatever the definition considered for exposure (prevalent or incident use, use of long- or short-acting molecule).

Key words: mortality, benzodiazepines, elderly, pharmacoepidemiology

Abstract #3: Benzodiazepine new use and long-term cognitive decline in the elderly: a prospective cohort study

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Objective: To evaluate the effect of benzodiazepine new-use on long-term cognitive decline in initially non-demented elderly patients.

Methods: A study was conducted in a cohort of elderly patients identified among participants in the prospective PAQUID study. Among benzodiazepine non-users at PAQUID inclusion, 167 benzodiazepine new-users and 1136 non-users, all free of dementia, were identified at follow-up year 3 (T_3). The evolution trend of their cognitive function was investigated using the Mini Mental State Examination (MMSE), the Isaacs Set Test (IST), and the Benton Visual Retention Test (BVRT) at follow-up visits conducted every 2-3 years after T_3. The association between benzodiazepine new-use and the evolution of cognitive performance was studied using a mixed model for curvilinear variables. These models were adjusted for age, sex, educational level, wine consumption, celibacy, dementia, and use of other psychotropic and cardiovascular drugs.

Results: Cognition levels appeared similar at baseline in T_3 between benzodiazepine new-users and non-users. Benzodiazepine new-users showed significantly lower cognitive levels as follow-up continued, according to IST (p=0.03). This cross-sectional effect of benzodiazepine new-use was weak (-0.35 after adjustment), as was the tendency observed for BVRT (-0.25, p=0.07). No longitudinal effect of benzodiazepine new-use was found whatever the cognitive test used, with the exception of a weak positive effect with the IST in sensitivity analyses.

Conclusions: Benzodiazepine new-use was not associated with a difference in cognitive evolution trend, despite users presenting globally lower cognitive performances over follow-up. Our study did not identify any specific effect of benzodiazepine new-use on cognitive decline in the elderly.

Key words: benzodiazepines, cognitive decline, dementia, pharmacoepidemiology, elderly

Abstract #4: Characteristics associated with psychotropic use in a French cohort of elderly farmers

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Background: Living in a rural area could account for some specificities leading to possible differences in what determinants of psychotropic use compared with the general population. Our aim was to evaluate the prevalence and characteristics of psychotropic use (in general and for the main families: benzodiazepines and antidepressants) in individuals living in a rural area of which little was known.

Methods: A cross-sectional study was conducted within AMI, a population-based cohort set up to study the ageing of a rural population. Between 2007 and 2009, 1002 subjects aged 65 years and over, living in rural areas in Gironde and retired from agricultural work after at least 20 years of activity, were randomly sampled from individuals registered in the agricultural Health Insurance programme (Mutualité Sociale Agricole, MSA). Analyses by multivariate logistic regression were used to evaluate the characteristics associated with psychotropic use.

Results: The AMI data at inclusion showed a lower prevalence of psychotropic use compared with what had been shown in the general population. This difference was less pronounced for men than women. Results from a multivariate logistic regression highlighted the characteristics associated with use already identified in the general population, such as: female gender, higher age (for benzodiazepines), lower age (for antidepressants), lower life-satisfaction, polypathologies, living in an institution, consumption of other psychotropics for benzodiazepine and antidepressant use. However, some specificities appeared: depressive disorders were more often associated with antidepressant than benzodiazepine use (Odds ratio, OR 3.78, 95% confidence interval 1.43 to 10.04 *versus* 1.68, 0.75 to 3.77), anxiety was associated with antidepressant use but not with benzodiazepine use (OR 2.32, 95%CI 1.17 to 4.62 *versus* 1.00, 0.65 to 1.55), a higher level of dependency was associated with a higher psychotropic consumption (OR 3.00, 95%CI 1.05 to 8.60, mainly antidepressants) but with an even lower consumption of benzodiazepines. Finally, cognitive disorders without dementia were associated with an even higher consumption of antidepressants but not of benzodiazepines.

Conclusion: This study highlights a lower use of psychotropics in elderly farmers compared to the general population and an apparently better compliance with good practice guidelines related to benzodiazepine and antidepressant indications.

Key words: psychotropic drugs, benzodiazepines, antidepressants, elderly, farmers

Abstract #5: Temporal trends of the characteristics associated with psychotropic use in a French cohort of elderly persons

C. Lacueille *MSc*[1 2], B. Bégaud *MD-PhD*[1 2 3], S. Billioti de Gage *PharmD-PhD candidate*[1 2], M. Tournier *MD-PhD*[1 2 3]

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Background: In France, the use of psychotropic drug is high, especially in the elderly. In recent decades, good practice guidelines have been published by government agencies to manage and optimise the prescription of psychotropic drugs, especially among the elderly. The objective of the study is to evaluate whether the characteristics associated with the use of psychotropic drugs changed between the period 1988-1998 and the period 2001-2008 in subjects aged 75 years and over.

Methods*:* The data are from the PAQUID cohort study carried out on 3777 subjects aged 65 years and over, living at home in the departments of Gironde and Dordogne. Analyses by multivariate logistic regression were used.

Results: In the two periods, more than half of the subjects consumed psychotropic drugs. The use of antidepressants more than doubled between the first and the second period. Factors such as being a woman, presenting with dementia or depression, being dependent, using more than nine drugs increased the probability of using psychotropic drugs.

Conclusion: We observed a few changes between the two periods regarding the use of psychotropic drugs and the use of the more specific classes of drug. These changes are in linked with health authority guidelines on the treatment of depression and the arrival on the market of new products.

Key words: psychotropic drugs, benzodiazepines, antidepressants, elderly

Annexes 2: Communications

1. Congress presentations

1.1. Oral communications

Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, Pariente A, Begaud B. Benzodiazepine use and risk of dementia: a case control study using the Quebec claims database. *13th ISoP (International Society of Pharmacovigilance) Annual Meeting* – Pise (Italy), October 2013.

Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, Pariente A, Begaud B. Benzodiazépines et risque de démence: étude cas-témoins. *12ème congrès de psychiatrie de l'ENCEPHALE* – Paris (France), January 2014. Congress award.

Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, Pariente A, Bégaud B. Increased risk of Alzheimer´s disease in benzodiazepine long-term users: a case-control study. *27th ECNP (European Neuropsychopharmacology) Congress* – Berlin (Germany), October 2014.

Billioti de Gage S, Benzodiazépines et risque de démence. Session thématique: usage et mésusage des benzodiazépines chez le sujet âgé. *7ème édition du CFP (Congrès Français de Psychiatrie)* – Lille (France), November 2015.

1.1. Poster presentations

Billioti de Gage S, Bégaud B, Verdoux H, Bazin F, Helmer C , Dartigues JF, A Pariente. Augmentation du risque de démence chez le sujet âgé consommateur de benzodiazépines: étude dans la cohorte PAQUID. VI*ème Congrès P2T (Physiologie, Pharmacologie et Thérapeutique)* – Grenoble (France), March 2011.

Billioti de Gage S, Bégaud B, Bazin F, Verdoux H, Dartigues JF, Peres K, T Kurth, A Pariente. Long-term increased risk of dementia in elderly benzodiazepines users. *11th ISoP (International Society of Pharmacovigilance) Annual Meeting* – Istanbul (Turkey), October 2011.

Billioti de Gage S, Bégaud B, Bazin F, Verdoux H, Dartigues JF, Peres K, T Kurth, A Pariente. Benzodiazepine use and risk of dementia: a prospective population based study. *28th ISPE (International Society of Pharmacoepidemiology) Annual Meeting* – Barcelone (Spain), August 2012.

Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, Pariente A, Bégaud B. Benzodiazepine use and risk of dementia: a case control study using the Quebec claims database. *29th ISPE (International Society of Pharmacoepidemiology) Annual Meeting* – Montreal (Canada), August 2013.

Marchand MS, Bégaud B, Billioti de Gage S, Pambrun E, Helmer C, Pariente, A. Initiation des benzodiazépines et déclin cognitif à long terme chez les sujets âgés: étude de cohorte prospective. *12ème congrès de psychiatrie de l'ENCEPHALE* – Paris (France), January 2014.

Pariente A, Billioti de Gage S, André M, Bégaud. Competing risks: why should we care about in pharmacoepidemiology reasearch? *IXème Congrès P2T (Physiologie, Pharmacologie et Thérapeutique* – Grenoble (France), April 2014.

Marchand MS, Bégaud B, Billioti de Gage S, Pambrun E, Helmer C, Pariente, A. Benzodiazepine new use and long-term cognitive decline in elderly : a prospective cohort study. *IXème Congrès P2T (Physiologie, Pharmacologie et Thérapeutique)* – Grenoble (France), April 2014.

Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, Pariente A, Bégaud B. Increased risk of Alzheimer´s disease in benzodiazepine long-term users: a case-control study. *27th ECNP (European Neuropsychopharmacology) Congress* – Berlin (Germany), October 2014.

2. Health authorities / Public health expertise

Bernard Bégaud B, Billioti de Gage S. Presentation of the preliminary results of the BENZODEM programme. *French Ministry of Health (Direction Générale de la Santé, DGS)* – Paris (france), June 2012.

Bernard Bégaud B, Billioti de Gage S. Presentation of the BENZODEM programme (assessment of the relationship between benzodiazepine use and the risk of dementia). *French Medicine Agency (Agence Nationale de Sécurité du Médicament, ANSM)* – Paris (France), November 2012.

3. Miscellaneous

Billioti de Gage S. Benzodiazépines et risque d'entrée en démence chez la personne âgée: présentation du problème, limites des connaissances, quantification du risque: étude de cohorte française. *Faculté de Pharmacie (Université de Montréal, Québec). Cours PHM 6156F "Pharmacovigilance" (responsable pédagogique, Yola Moride)* – Montreal (Canada), June 2011.

Billioti de Gage S. Exposition aux Benzodiazépines et risque de démence chez la personne âgée: étude de cohorte à partir des données de l'étude PAQUID. *8e journée INSERM U657* – Bordeaux (France), February 2012.

Billioti de Gage S. Psychotropes et déclin cognitif dans la population âgée. *Master 2 Pharmaco-épidémiologie/ Pharmacovigilance (Université de Bordeaux). UE "pharmaco-épidémiologie des médicaments psychotropes" (responsable pédagogique, Marie Tournier).* 2012-2014.

Billioti de Gage S. "Consommation de psychotropes, démence et dépendance d'origine psychique tout au long du processus démentiel dans le cadre de trois cohortes en population : PAQUID, 3C et AMI". Présentation du projet, études en cours et projections - *Séminaire IReSP (Institut de Recherche en Santé Publique* – Paris (France), November 2012.

Billioti de Gage S. Benzodiazépines et démence chez les personnes âgées: étude de cohorte. *2e Journées de l'Ecole Doctorale Sociétés, Politique, Santé publique* – Villenave d'Ornon (France), May 2013.

Billioti de Gage S. Benzodiazépines et addictions. *Réseau BASTHA (Bassin d'Arcachon, SIDA, Toxicomanie, Hépatites, Addictions)* – Arcachon (France), December 2013.

Billioti de Gage S. Benzodiazépines et démence. *Journées régionales Fédération Addiction, ARS, GRRITTA (Groupe Régional de Recherche et de Réflexion des Intervenants en Toxicomanie et Addictologie d'Aquitaine).* Bordeaux (France), January 2014.

Billioti de Gage S. « Consommation de psychotropes, démence et dépendance d'origine psychique tout au long du processus démentiel dans le cadre de trois cohortes en population : PAQUID, 3C et AMI ». Résultats du projet, études en cours et projections – *Séminaire de clôture de l'IReSP (Institut de Recherche en Santé Publique)* – Paris (France), November 2014.

Annexes 3: Public Health communications

1. Haute Autorité de Santé (HAS): hypnotics

25 septembre 2012 | Dossier de Presse
Troubles du sommeil : stop à la prescription systématique de somnifères chez les personnes âgées

Après 65 ans, le sommeil évolue : nuits plus courtes, réveils plus fréquents, sommeil fractionné sur la journée, ... Ces modifications d'ordre physiologique chez les personnes âgées sont source de plaintes du sommeil en consultation et débouchent trop souvent sur une prescription de somnifères. Près d'un tiers des personnes de plus de 65 ans consomme des somnifères de manière chronique, et dans plus d'un cas sur deux, ces traitements ne seraient pas indiqués. Ces somnifères peuvent provoquer des effets délétères : dépendance, chutes et troubles de la mémoire. Quel sommeil après 65 ans ? Comment aborder la question des troubles du sommeil en consultation ? Quel usage des somnifères ? Comment les arrêter ? Avec quel accompagnement ? Est-il possible de retrouver un sommeil de qualité sans médicament ?

Pour diminuer la prescription trop systématique de somnifères chez les personnes âgées, la Haute Autorité de Santé (HAS) a élaboré, dès 2006, avec des médecins généralistes, des gériatres, des psychiatres, des spécialistes du sommeil et des pharmaciens, des recommandations et des outils pour aider les professionnels de santé et informer les patients. Parce que la consommation ne diminue pas suffisamment et que de nombreuses prescriptions ne sont pas utiles, la HAS relance des actions d'information et de sensibilisation des professionnels et des usagers avec le soutien du Conseil National de l'Ordre des Médecins (CNOM), du Conseil National de l'Ordre des Pharmaciens (CNOP) et de l'association de lutte contre les infections nosocomiales et les accidents médicaux (LIEN) membre du Collectif interassociatif sur la santé (CISS).

Seules 1 à 2 plaintes relatives au sommeil sur 10 relèveraient de l'insomnie véritable

Le sentiment de « mal dormir » pousse de nombreuses personnes âgées à se plaindre d'insomnie, sans que cela en soit véritablement une. La plainte du sommeil chez la personne âgée doit faire l'objet d'un entretien spécifique lors d'une consultation dédiée. Pour aider les médecins dans cette démarche diagnostique, la HAS a élaboré des outils pratiques, comme par exemple des arbres décisionnels, des questions clés pour la prescription de psychotropes, un agenda du sommeil, un questionnaire d'attachement aux benzodiazépines, …

Devant des plaintes chroniques du sommeil, le médecin doit rechercher des signes associés et orienter son patient vers un spécialiste si besoin : douleurs, anxiété, dépression ou encore problèmes urinaires, apnée du sommeil peuvent expliquer le sommeil de mauvaise qualité et doivent être recherchés. Par ailleurs, la plainte du sommeil peut être expliquée par le changement physiologique du sommeil : la personne âgée dort moins la nuit et son sommeil se répartit différemment sur l'ensemble de la journée (siestes par exemple). Seules 10 à 20% des plaintes du sommeil sont de véritables insomnies et peuvent alors relever d'un traitement par somnifères, mais toujours de courte durée, en prévoyant l'arrêt dès la prescription. Les techniques de relaxation et les thérapies cognitivo-comportementales peuvent être appropriées à la prise en charge des insomnies.

La moitié des traitements ne serait pas indiquée

La HAS rappelle aux médecins, aux pharmaciens et aux patients que la prescription et le renouvellement de somnifères ne doivent pas être systématiques. Les somnifères ne sont indiqués que pour de courtes périodes et dans un délai allant de quelques jours à 4 semaines maximum. Ils ne doivent pas être prescrits sur une longue durée, ce d'autant plus que leur efficacité diminue avec le temps. De plus, ils induisent des effets indésirables : chutes, risques d'accidents lors de la conduite, troubles de la mémoire ou de l'attention, dépendance, …. Les personnes âgées sont d'autant plus exposées aux risques des somnifères que leur résistance physique est moindre et leur métabolisme plus lent. Par ailleurs, le risque d'interaction avec d'autres traitements est augmenté car les personnes âgées prennent souvent plusieurs médicaments.

Arrêter les somnifères, c'est possible !

Le médecin traitant doit proposer une stratégie d'arrêt des somnifères en accord avec le patient. L'arrêt progressif et encadré de somnifère doit permettre aux personnes âgées de retrouver un sommeil naturel, plus récupérateur, même s'il est plus court ou plus fractionné. En ne subissant plus les effets secondaires du médicament, les personnes âgées gagnent en qualité de vie et en autonomie.

Une bonne hygiène de vie pour améliorer naturellement le sommeil

Les somnifères ne sont pas des médicaments anodins. Les changements de rythme du sommeil liés au vieillissement peuvent être améliorés par des habitudes simples et une bonne hygiène de vie : activités physiques régulières, exposition à la lumière en journée, alimentation et mode de vie sains, aménagement confortable de la chambre, …

Un programme d'actions et des outils relayés par les partenaires de la HAS

Dans les prochaines semaines, le CNOM et le CNOP relaieront les outils de la HAS et notamment l'affiche « Etre senior et mieux dormir », conseils pour bien dormir aux médecins et pharmaciens. Le LIEN quant à lui relaiera l'information sur son site internet. La HAS relaiera pour sa part ces informations sur son site, dans ses lettres destinées aux professionnels et sur son espace Facebook®. En novembre, la HAS organise une plénière nationale avec l'ensemble des professionnels de santé impliqués et les patients afin de renforcer la diffusion de l'information et réfléchir à de nouvelles actions et outils d'amélioration des pratiques. D'ici la fin de l'année, un rappel sera intégré aux logiciels d'aide à la prescription (LAP) et sera associé à des documents d'information des patients sur le sommeil et les somnifères. Ainsi, à chaque fois qu'un médecin prescrira un somnifère à une personne âgée, il sera, par exemple, invité à proposer à son patient un rendez-vous dédié à l'exploration de ses problèmes de sommeil.

Les somnifères… en finir avec les mauvaises habitudes !

- La prescription ou le renouvellement d'un somnifère n'est pas systématique.
- Le renouvellement d'une ordonnance nécessite la réévaluation de la situation clinique du patient.
- L'association de deux somnifères n'est pas recommandée.
- Une pathologie psychiatrique (dépression par exemple) ou une pathologie du sommeil (apnée du sommeil par exemple) peuvent être à l'origine de la plainte du sommeil et nécessitent une prise en charge adaptée.
- L'arrêt brutal d'une prescription de somnifères n'est pas recommandé, l'arrêt doit être progressif avec un suivi médical.

2. Agence France Presse (AFP) communication: BENZODEM

La prescription de benzodiazépines doit être "la plus courte possible" (ANSM)

PARIS, 17 déc 2012 (AFP) - La prescription de benzodiazépines, des médicaments utilisés contre l'anxiété et l'insomnie, doit être "la plus courte possible", a rappelé lundi l'agence du médicament ANSM.

La nouvelle mis en garde survient à la suite de deux études, dont l'une de l'Inserm faisant état d'un risque accru de démence chez les personnes âgées de plus de 65 ans qui prennent ces médicaments.

Selon l'étude réalisée par Bernard Bégaud (Inserm/Université de Bordeaux) et Tobias Kurth, le risque serait augmenté de 50% par rapport aux personnes n'ayant jamais consommé de benzodiazépines.

"Cette association (entre benzodiazépines et démence), bien que de faible intensité, vient s'ajouter aux autres risques déjà identifiés", relève dans un point d'information l'ANSM qui reconnaît que les données disponibles à ce stade "ne permettent pas d'établir une relation entre la dose, la durée et l'effet".

La France est l'un des pays qui consomme le plus de benzodiazépines, avec une utilisation record chez les plus de 65 ans qui sont 30% à prendre ces médicaments, contre 20% en Espagne ou au Canada et 15% en Australie.
Pour réduire cette consommation, l'ANSM rappelle que la prescription ne doit être envisagée qu'après l'échec des approches médicamenteuses et qu'elle doit "être la plus courte possible", 4 semaines au maximum pour les hypnotiques (somnifères) et 12 semaines pour les anxiolytiques.

La durée moyenne de prescription des somnifères est de 7 mois dans la population générale, mais nettement plus importante chez les plus de 65 ans, comme le rappelait récemment la Haute Autorité de santé (HAS).
Ces médicaments ont des effets indésirables importants, notamment chez les patients les plus âgés, avec des chutes, des troubles de la mémoire et une dépendance au médicament.

L'agence du médicament rappelle également que la prescription de benzodiazépines doit être réévaluée régulièrement par les médecins "quant à son efficacité et ses effets indésirables" et que le patient doit être informé des risques liées à cette consommation, notamment du risque de dépendance.

L'ANSM envisage par ailleurs d'étendre la prescription sur ordonnances sécurisées - qui ont remplacé les carnets à souche pour les médicaments classés comme stupéfiants - à l'ensemble des benzodiazépines. Toutefois, l'agence sanitaire précise qu'elle attend les résultats d'une enquête auprès des professionnels, qui seront disponibles début 2013, pour évaluer la pertinence de cette mesure.

ez/BC/fa/bma

3. Action plan to reduce benzodiazepine misuse (ANSM, September 2012)

ansm
Agence nationale de sécurité du médicament et des produits de santé

Point d'Information

Plan d'actions de l'ANSM visant à réduire le mésusage des benzodiazépines

Les dispositifs d'information existants ainsi que les études menées dans le champ de l'utilisation des benzodiazépines, montrent que leur consommation en France reste l'une des plus importantes de l'Union Européenne et qu'une large part est utilisée en dehors du cadre de l'autorisation de mise sur le marché (AMM). Sur la base du rapport d'expertise publié au mois de janvier 2012, l'Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM), s'est engagée dans un plan d'actions visant à renforcer la surveillance et la lutte contre le mésusage des médicaments de la classe des benzodiazépines, à favoriser leur bon usage et à limiter leur surconsommation et les risques qui lui sont liés. Ce plan comprend aussi bien l'analyse de données scientifiques que des mesures d'ordre réglementaire et des actions d'information et de communication auprès des professionnels de santé.

Le rapport dressant un état des lieux de la consommation des benzodiazépines en France[1] réalisé par l'ANSM à partir de différentes sources (données de l'Assurance Maladie, données issues d'enquêtes des réseaux de vigilance de l'Agence, enquêtes sur des populations particulières) montre que la consommation de benzodiazépines par la population française reste très importante, même si cette consommation est en diminution (en 2010, 20% de la population a consommé au moins une fois une benzodiazépine). Il montre également que la durée médiane de traitement est de 7 mois et qu'environ la moitié des sujets traités le sont depuis plus de 2 ans. Ce rapport met également en exergue que les risques liés à leur usage persistent.

Quelles sont les actions déjà entreprises par l'ANSM concernant les benzodiazépines ?

- **Surveillance sanitaire**

L'ensemble des benzodiazépines fait l'objet d'une surveillance continue par les réseaux de pharmacovigilance et d'addictovigilance de l'Agence. Un plan de gestion des risques a également été mis en place pour le Rivotril®.

Certains risques liés à des situations particulières sont également examinés par l'Agence. C'est le cas notamment de l'utilisation des benzodiazépines en milieu professionnel ou dans le cadre de la conduite automobile. Une importante étude pharmaco-épidémiologique soutenue par l'Agence dans ce dernier champ - et qui se poursuit - a ainsi mis en évidence un lien hautement significatif entre consommation de benzodiazépines et survenue d'accidents de la route.

- **Encadrement et sécurisation de la prescription et de la délivrance**

La durée maximale de prescription des benzodiazépines anxiolytiques est limitée à 12 semaines et celle des hypnotiques à 4 semaines. Elle a été réduite de façon plus importante pour certains médicaments hypnotiques pour en limiter leur mésusage. C'est le cas du flunitrazépam (Rohypnol®), dont la durée maximale de prescription a été limitée à 14 jours en 2001. De la même manière, la restriction de la durée maximale de prescription a été un levier pour limiter l'abus du clonazépam (Rivotril®) avec la mise en place d'une limitation à 12 semaines depuis 2010. La restriction récente de prescription aux neurologues et/ou aux pédiatres depuis 2012 est une mesure qui entre également dans ce champ. Pour certaines benzodiazépines particulièrement détournées, notamment par les toxicomanes (Rivotril®, Rohypnol®, Tranxène®), la prescription sur ordonnance sécurisée a été rendue obligatoire.

[1] Etat des lieux de la consommation des benzodiazépines en France, Rapport d'expertise de l'Afssaps, Janvier 2012.
http://ansm.sante.fr/var/ansm_site/storage/original/application/3f1dc4756b5bc091879c9c254d95e05c.pdf

Par ailleurs, les résumés des caractéristiques du produit (RCP) et les notices des benzodiazépines ont été harmonisés depuis 2004. La notion de pharmacodépendance y est mentionnée pour toutes les spécialités.

- **Prévention du risque de soumission chimique et d'abus**

Certaines modifications galéniques ont été apportées à plusieurs benzodiazépines pour limiter le risque de soumission chimique (colorant pour le Rohypnol® par exemple). Les tailles de conditionnement ont aussi été réduites pour limiter les risques d'abus (Rohypnol®, Rivotril®).

- **Amélioration de l'information des professionnels de santé et des patients**

Différentes actions de communication ont été réalisées par l'Agence. Il s'agit par exemple de la diffusion de lettres d'information aux professionnels de santé mais aussi de communiqués ou de points d'information mis en ligne sur le site de l'Agence comme celui sur le Rivotril® (bon usage/modification des conditions de prescription et de délivrance) ou sur le Rohypnol®. Ces publications (rapport sur les benzodiazépines, mentionné ci-dessus, mise au point sur l'arrêt des hypnotiques, mise au point sur l'arrêt d'utilisation hors AMM du Rivotril®) et leur diffusion permettent d'informer un nombre toujours plus grand de professionnels de santé.

La mise en place depuis 2005 des pictogrammes apposés sur les conditionnements externes des médicaments susceptibles d'altérer les capacités à conduire un véhicule permet de rappeler la dangerosité potentielle de ces molécules (les benzodiazépines relevant des niveaux de risque les plus élevés).

Quelles sont les actions que l'ANSM va entreprendre concernant les benzodiazépines ?

Si ces mesures déjà mises en place ou initiées par l'ANSM ont permis de stabiliser voire de diminuer la consommation de benzodiazépines et de favoriser leur bon usage, des axes complémentaires d'action sont envisagés pour favoriser le bon usage de ces molécules et mieux surveiller leurs effets indésirables. Les actions de ce plan sont entreprises en concertation et en cohérence avec celles menées par d'autres institutions.[2]

- **Des mesures réglementaires**

Sécurisation de la prescription

L'extension de la prescription de l'ensemble des benzodiazépines sur ordonnance sécurisée est une des pistes d'action. Les résultats de l'enquête sur les ordonnances sécurisées réalisée auprès des professionnels de santé et dont les résultats devraient être disponibles avant la fin de l'année 2012 seront un des éléments de la prise de décision.

Réduction de la taille des conditionnements

Une réduction de la taille des conditionnements de certaines benzodiazépines pourrait également être retenue, puisque les conditionnements actuels ne sont pas tous adaptés à une prescription courte ou à la durée maximale de prescription prévue.

- **Une communication vers les professionnels de santé à poursuivre**

L'information des prescripteurs, en particulier celle des médecins généralistes qui réalisent près de 90% de prescriptions, est primordiale. Certains messages essentiels pourraient être rappelés comme la nécessité de « peser » la première prescription, de limiter les posologies et la prescription dans le temps, de ne pas associer plusieurs benzodiazépines entre elles et de réévaluer régulièrement la pertinence du traitement.

- **Les benzodiazépines sous surveillance**

La surveillance de ces molécules, déjà existante *via* les enquêtes menées par les différents réseaux de surveillance de l'Agence mais aussi *via* les données de remboursement de l'Assurance Maladie, les données en pharmaco-épidémiologie ou encore celles issues des plans de gestion de risque, est poursuivie. Le rapport émis par l'Agence début 2012 sur la consommation des benzodiazépines sera réactualisé régulièrement.

L'Agence souhaite pouvoir analyser plus précisément le lien suspecté entre prise de benzodiazépines et démence (maladie d'Alzheimer en particulier). Ceci, en s'appuyant sur les travaux du groupe d'épidémiologistes qu'elle a mis en place, qui réalisera notamment une analyse des résultats de l'étude

[2] http://www.has-sante.fr/portail/upload/docs/application/pdf/2012-09/des_mesures_contre_le_mesusage_des_benzodiazepines_has_-_dgs_-_ansm.pdf

http://www.has-sante.fr/portail/jcms/c_1299994/troubles-du-sommeil-stop-a-la-prescription-systematique-de-somniferes-chez-les-personnes-agees

« Benzodem », qui devraient être publiés début octobre, ainsi que de toutes les autres données disponibles depuis un an.

- **Des mesures à envisager au niveau européen**

L'ANSM portera la question du lien entre benzodiazépines et démence devant l'agence européenne du médicament (EMA) pour aboutir à une expertise partagée sur le profil de sécurité de ces molécules. Si le niveau de preuve est suffisant, une modification de la notice et du RCP pourrait être mise en œuvre afin d'informer les prescripteurs et les patients de ce risque.

4. Letter to prescribers (ANSM, December 2012)

ansm
Agence nationale de sécurité du médicament et des produits de santé

RÉPUBLIQUE FRANÇAISE

Mise en garde

Décembre 2012

Benzodiazépines et démence : limiter les risques par un strict respect des règles de prescription et de bon usage

Information destinée aux médecins généralistes, neurologues et psychiatres.

Madame, Monsieur, cher Confrère,

L'Agence nationale de sécurité du médicament et des produits de santé (ANSM), souhaite vous rappeler les règles de prescription et de bon usage des benzodiazépines et vous mettre en garde sur les risques potentiels liés à leur utilisation.

Cette information fait suite à la publication récente de l'étude « Benzodem » dirigée par le Pr Bernard Bégaud[1] et de résultats préliminaires des travaux du Pr Christophe Tzourio (Etude des Trois-Cités - 3C). L'étude « Benzodem » confirme l'existence, chez les personnes âgées de plus de 65 ans vivant à domicile, d'une association entre la prise de benzodiazépines et le risque de démence. Ces résultats sont cohérents et convergents avec les données préliminaires de l'étude des « 3C ». S'il est important de rappeler que ces études épidémiologiques observationnelles ne peuvent pas mettre en évidence avec une certitude suffisante un lien de causalité entre la prise des benzodiazépines et la survenue d'une démence, cette association, de faible intensité, vient s'ajouter aux autres risques déjà identifiés.

Les benzodiazépines ont démontré leur utilité thérapeutique en particulier en tant qu'anxiolytique et hypnotique lorsqu'elles sont correctement utilisées. Par conséquent, l'Agence souhaite attirer votre attention sur les règles de prescription et de bon usage des benzodiazépines :

- La prescription des benzodiazépines à visée anxiolytique et hypnotique ne doit être envisagée qu'après échec des approches non médicamenteuses.
- La première prescription chez un patient est une prescription à risque qui peut entraîner le patient dans un processus de consommation de longue durée, alors que l'effet thérapeutique sera épuisé.
- Cette prescription doit être la plus courte possible et ne doit pas dépasser les durées préconisées dans l'AMM. Elle doit être régulièrement réévaluée quant à son efficacité et ses effets indésirables.
- Le patient doit être informé des risques liés à cette consommation et accompagné dans l'arrêt de sa consommation dont on sait qu'il peut être difficile quand la dépendance est installée[2] [3].

L'ANSM a entrepris différentes actions pour renforcer la sécurité d'emploi des benzodiazépines. La surveillance continue de ces molécules *via* les réseaux de pharmacovigilance et d'addictovigilance de l'Agence en fait partie. L'encadrement et la sécurisation de la prescription et de la délivrance de certaines benzodiazépines (ordonnances sécurisées obligatoires ou restrictions de durées de prescription notamment) en fait également partie tout comme l'amélioration de l'information faite aux professionnels de santé et aux patients dans ce champ.
L'Agence envisage de poursuivre ces actions de surveillance, de sécurisation et d'information relatives à ces molécules et prévoit également de porter les réflexions actuelles sur les benzodiazépines et les risques de démence au niveau de l'Agence européenne du médicament (EMA).

Je vous prie de croire, Madame, Monsieur, cher Confrère, en l'expression de mes salutations distinguées.

Pr Dominique MARANINCHI
Directeur général de l'ANSM

Inscrivez-vous à la nouvelle newsletter mensuelle de l'ANSM : ANSM Actu (www.ansm.sante.fr)

[1] Billioti de Gage S, Bégaud B, Bazin F, Verdoux H, Dartigues JF, Pérès K, Kurth T, Pariente A. Benzodiazepine use and risk of dementia: prospective population based study. BMJ. 2012 ;345:e6231.
[2] Renvoi sur la mise au point de l'ANSM sur l'arrêt du Rivotril® per os utilisé hors AMM (18/10/11) : http://ansm.sante.fr/var/ansm_site/storage/original/application/3de3f45af94fd63d325939f129f018f1.pdf
[3] Renvoi sur les recommandations émises par la HAS sur l'arrêt des benzodiazépines chez les sujets âgés (Octobre 2007) : http://www.has-sante.fr/portail/jcms/c_601509/modalites-d-arret-des-benzodiazepines-et-medicaments-apparentes-chez-le-patient-age

Liste indicative des benzodiazépines commercialisées et de leurs conditions de prescription et de délivrance

Substance active	Nom des spécialités commercialisées	Ordonnance sécurisée	Durée maximale de prescription
Anxiolytiques			
Alprazolam	Xanax et génériques	non	12 semaines
Bromazépam	Lexomil et génériques	non	12 semaines
Clobazam	Urbanyl	non	12 semaines
Clorazépate potassique < 20 mg, voie orale	Tranxène	non	12 semaines
Clorazépate potassique ≥ 20 mg, voie orale	Tranxène	**OUI**	28 jours
Clotiazépam	Vératran	non	12 semaines
Diazépam	Valium	non	12 semaines
Ethyl loflazépate	Victan	non	12 semaines
Lorazépam	Témesta et génériques	non	12 semaines
Nordazépam	Nordaz	non	12 semaines
Oxazépam	Séresta et génériques	non	12 semaines
Prazépam	Lysanxia et génériques	non	12 semaines
Hypnotiques			
Estazolam	Nuctalon	non	4 semaines
Flunitrazépam	Rohypnol	**OUI**	14 jours avec délivrance fractionnée de 7 jours
Loprazolam	Havlane	non	4 semaines
Lormétazépam	Noctamide	non	4 semaines
Nitrazépam	Mogadon	non	4 semaines
Témazépam	Normison	non	4 semaines
Apparentés aux benzodiazépines			
Zolpidem	Stilnox et génériques	non	4 semaines
Zopiclone	Imovane et génériques	non	4 semaines
Myorelaxant			
Tétrazépam	Myolastan et génériques	non	12 mois
Anticonvulsivant			
Clonazépam	Rivotril	**OUI**	12 semaines

5. French reports about benzodiazepine use

ANSM (Agence Nationale de sécurité du Médicament). Etat des lieux de la consommation de benzodiazepines en France. Décembre 2013.
http://ansm.sante.fr/content/download/57511/738785/version/2/file/ANSM_Rapport+Benzo_09012014.pdf

ANSM (Agence Nationale de sécurité du Médicament). Etat des lieux de la consommation de benzodiazepines en France. Janvier 2012.
http://ansm.sante.fr/var/ansm_site/storage/original/application/3f1dc4756b5bc091879c9c254d95e05c.pdf

6. Agence de Presse Médicale (APM) Communication: BENZODEM2 (January 2014)

SUJET : PSYCHIATRIE-SANTE MENTALE NEURO GERONTO ALZHEIMER-DEMENCES VIGILANCE BON USAGE-HORS AMM DEPRESSION-ANXIETE CONGRES

Une prise prolongée de benzodiazépines associée au risque de démence chez les plus de 65 ans.

PARIS, 23 janvier 2014 (APM) - Les personnes de plus de 65 ans qui prennent de manière prolongée des benzodiazépines présentent un risque accru de développer une démence, suggère une nouvelle étude présentée jeudi au congrès de l'encéphale à Paris.

Ces résultats, issus d'une analyse des données de l'assurance maladie du Québec, confortent un "soupçon" d'un lien entre benzodiazépine et démence, avait commenté auprès de l'APM le Pr Bernard Bégaud directeur de l'Inserm U657 à l'université de Bordeaux, coordonnateur de cette étude, à l'occasion du rapport 2013 de l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) sur la consommation de ces traitements en France (cf APM LDRA9004).

Les données, qui sont soumises à publication, sont présentées jeudi en session orale du congrès organisé par la revue médicale de psychiatrie clinique biologique et thérapeutique.
Dans le résumé de leur communication, Sophie Billioti de Gage de l'U657 et ses collègues indiquent que l'évaluation de la réalité du risque de démence paraît "majeure" en raison de la prévalence élevée et de la gravité de cette maladie ainsi que de l'usage répandu et chronique de ces médicaments.

Pour rechercher la vraisemblance d'un lien causal entre consommation de benzodiazépines et risque de démence chez les personnes âgées, ils ont mené une étude cas-témoin dans un échantillon de personnes de plus de 65 ans suivies au moins six ans, en utilisant les données de remboursement de l'assurance maladie du Québec.

Ils ont identifié 1.796 personnes avec un diagnostic de maladie d'Alzheimer et apparié pour chacun quatre témoins, soit 7.184 personnes, sur l'âge, le sexe et la durée de suivi.

La durée d'exposition aux benzodiazépines durant les cinq à 10 années précédant le diagnostic de démence a été examinée, quel que soit le type de médicament d'abord puis en tenant compte de la dose cumulée utilisée et la demi-vie d'élimination des molécules (courte ou longue, c'est-à-dire inférieure ou supérieure à 20 heures).

L'analyse multivariée des données montre une association statistiquement significative entre l'exposition aux benzodiazépines et un risque de démence, avec un risque relatif rapproché (OR) de 1,51.

Il apparaît une relation dose-dépendante: le risque de démence n'était pas associé à des doses cumulées correspondant à un à 90 jours d'utilisation mais l'était au-delà, avec un OR significatif de 1,32 pour une exposition de 91 à 180 jours et de 1,84 pour plus de 180 jours.

De manière similaire, l'OR entre démence et benzodiazépines était de 1,67 pour les molécules de demi-vie courte et de 1,93 pour celles de demi-vie longue.

L'ajustement sur anxiété et dépression, des "potentiels prodromes de démence", n'a pas modifié les résultats.

"Cette augmentation du risque de démence chez les consommateurs prolongés de benzodiazépines, restant significative malgré l'ajustement sur anxiété et dépression et augmentant avec la densité de l'exposition, plaide en faveur d'une association causale et devrait inciter au respect des bonnes pratiques", concluent les auteurs.

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7. Agence de Presse Médicale (APM) communication: benzodiazepines and cognitive decline (April 2014)

Objet : L'initiation d'un traitement par benzodiazépine chez les personnes âgées non associée au déclin cognitif (hors démence)

POITIERS, 28 avril 2014 (APM) - L'initiation d'un traitement par benzodiazépine chez des personnes âgées n'est pas associée à un déclin cognitif, selon une étude pharmaco-épidémiologique française qui a été présentée la semaine dernière au congrès de physiologie, pharmacologie et thérapeutique (P2T) à Poitiers.

Cette étude, conduite par l'équipe de Bernard Bégaud à l'université de Bordeaux et à l'Inserm à partir de la cohorte PAQUID, pourrait paraître contradictoire avec les résultats antérieurs de ces chercheurs montrant un lien entre les benzodiazépines et le risque de démence (APM LDOIT001 et APM LDRAN001). Mais, interrogé par l'APM, le Pr Bégaud explique qu'il n'en est rien et qu'au contraire cela renforce leurs conclusions.

Dans l'étude présentée à Poitiers par Marie-Sara Marchand, les chercheurs ont comparé 167 personnes de 65 ans et plus ayant débuté un traitement par benzodiazépine et 1.136 personnes qui ne prenaient pas ces médicaments. Ils se sont intéressés au risque de déclin cognitif, mesuré par les tests MMSE (Mini Mental State Examination) et IST (Isaacs Set test).

L'initiation d'un traitement par benzodiazépine n'a eu aucun effet sur le déclin cognitif, ont constaté les auteurs.

Ces résultats "ne sont pas contradictoires" avec ceux montrant un lien entre les benzodiazépines à l'augmentation de risque de démence, indique le Pr Bégaud à l'APM. Tout d'abord, il rappelle que "toute altération cognitive ne signe pas le développement d'une démence".

Ensuite, cette étude permet d'écarter certaines objections qui étaient faites aux travaux montrant un lien entre ces médicaments et les démences. C'est notamment le cas du "biais protopathique", c'est-à-dire le fait que les benzodiazépines seraient prescrites pour des symptômes qui seraient en réalité les premiers signes d'une démence. En se centrant sur des patients qui débutaient un traitement par benzodiazépine, les chercheurs ont vérifié qu'à l'initiation du traitement ces patients n'avaient pas d'altération cognitive.

De même, une autre objection était que, dans les études antérieures, certaines démences n'auraient pas été de vraies démences mais seulement des altérations cognitives. Là aussi, la nouvelle étude montre que ça n'est pas le cas puisqu'aucune altération cognitive n'était augmentée avec les benzodiazépines.

"L'association benzodiazépines-démences existe bien, au sens statistique", estime donc Bernard Bégaud. Mais une question reste encore non résolue, reconnaît-il, celle du mécanisme derrière cette association statistique.

Le chercheur bordelais ne pense pas qu'il y ait un effet direct des benzodiazépines, mais avance deux hypothèses. L'une est que les benzodiazépines, traitement de l'anxiété, seraient un marqueur du fait que les personnes ayant des problèmes d'anxiété récurrents seraient ensuite à plus haut risque de démence.

Bien que, selon cette hypothèse, elles n'auraient pas de responsabilité dans la survenue de la démence, cela serait "tout de même intéressant" car on pourrait ainsi identifier précocement des personnes ayant un risque augmenté, note-t-il.

L'autre hypothèse est que les benzodiazépines "amputeraient la réserve cognitive". De nombreuses études suggèrent que la stimulation intellectuelle permet de retarder l'apparition d'une démence, probablement en favorisant une certaine plasticité cérébrale. Il est possible que les benzodiazépines aient un effet inverse: par leur effet pharmacologique, elles diminueraient la mobilisation de cette réserve cognitive, accélérant alors la survenue de la démence.

"Nous avons une troisième théorie qui est un 'mix' des deux précédentes", indique Bernard Bégaud. Il souhaite continuer à travailler sur ce sujet, notamment en conduisant des études sur de grandes cohortes qui suivraient des personnes dès un âge de 30-40 ans pour détecter plus précocement dans la vie un possible lien entre anxiété et dépression et risque ultérieur de démence.

Mais il déplore les difficultés à trouver des financements, ce qui lui apparaît regrettable que si ses travaux débouchaient sur un moyen de retarder la survenue de démences, cela aurait un bénéfice pour les patients et leurs familles et permettrait de faire des économies importantes.

8. Agence de Presse Médicale (APM) communication: reduction of hypnotic reimbursement

SUJET : PSYCHIATRIE-SANTE MENTALE NEURO SOMMEIL VIGILANCE HAS ANSM-AFSSAPS GERONTO VIGILANCE BON USAGE-HORS AMM DGS ASSURANCE MALADIE

La HAS recommande une baisse du taux de remboursement des hypnotiques

PARIS, 24 juillet 2014 (APM) - La Commission de la transparence (CT) a revu à la baisse le service médical rendu (SMR) de sept benzodiazépines et molécules apparentées dans l'insomnie, recommandant une baisse de leur niveau de remboursement à 15%, a annoncé la Haute autorité de santé (HAS), jeudi dans un communiqué.

Cette réévaluation s'inscrit dans un plan d'actions lancé en 2012 par la Direction générale dela santé (DGS), avec la HAS et l'Agence nationale de sécurité du médicament et des produitsde santé (ANSM) contre le mésusage des benzodiazépines, rappelle la HAS.

Dans "cette démarche de prévention", la CT "a positionné au plus bas niveau d'intérêt" les benzodiazépines hypnotiques et produits apparentés, considérant leur SMR "faible" dans le traitement des "troubles sévères du sommeil dans les cas suivants: insomnie occasionnelle, insomnie transitoire".

"Sur une longue période, la faible efficacité de ces médicaments sur la durée du sommeil,leurs effets délétères et le mésusage constaté ont conduit la CT à conclure à un intérêt thérapeutique limité de ces médicaments", note la HAS.

"Ce constat devrait entraîner une diminution du taux de remboursement à 15%, contre 65% auparavant", ajoute-t-elle.

Les molécules concernées sont les cinq benzodiazépines estazolam (Nuctalon*, Takeda),loprazolam (Havlane*, Sanofi), lormétazépam (Noctamide*, Bayer, et génériques), nitrazépam (Mogadon*, Meda Pharma) et témazépam (Normison*, Primius Lab), ainsi que les deux hypnotiques apparentés zolpidem (Stilnox*, Sanofi, et génériques) et zopiclone (Imovane*,Sanofi, et génériques).

La CT préconise également dans le communiqué de prescrire la plus faible dose et pour la plus courte période possible, en seconde intention après échec des thérapies cognitivocomportementales.

Dans les sept avis datés du 25 juin, la CT recommande également de renforcer la formation initiale des professionnels de santé sur le bon usage des benzodiazépines et leurs modalités d'arrêt, et de soutenir les mesures qui pourront être préconisées par l'ANSM, dans le cadre de ses missions pouvant permettre une meilleure utilisation de ces produits.

Elle préconise de développer l'usage et l'accès aux prises en charge

non médicamenteuses,notamment les thérapies cognitivo comportementales.
Une meilleure information du public sur les risques de l'utilisation chronique de ces médicaments et sur leur bon usage est nécessaire via "une campagne médiatique percutante et répétée", souligne-t-elle.

Environ 4 millions de personnes sont exposées aux benzodiazépines hypnotiques ou molécules apparentées en France, selon l'extrapolation des données de l'échantillon généraliste des bénéficiaires de l'assurance maladie, rappelle la HAS.

Selon les données de vente du Groupement pour l'élaboration et la réalisation de statistiques (Gers), 48,8 millions de boîtes de benzodiazépines hypnotiques et molécules apparentées ont été vendues en officine en 2013. Le zopiclone et le zolpidem représentent 81% des ventes.

La consommation des benzodiazépines a repris en 2012 en France après une période de stabilité, selon un état des lieux publié en janvier par l'ANSM (cf APM LDRA8002).

Après plusieurs actions auprès des prescripteurs et des patients, les autorités préparent des "mesures d'ordre réglementaire" (obligation de prescription sur ordonnances sécurisées, diminution des conditionnements...) qui sont encore "en cours de discussion", ajoute la HAS dans les différents avis.

Le flunitrazépam (Rohypnol*, Roche) est également réévalué car, même si le laboratoire a décidé de ne plus le commercialiser (cf APM SOQDJ003), l'AMM dans la prise en charge des troubles sévères du sommeil reste valide. En raison des alternatives disponibles et de l'usage détourné de ce médicament, la CT s'est déclarée défavorable au maintien au remboursement de cette benzodiazépine.

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9. Agence France Presse (AFP) communication: BENZODEM2 (September 2014)

Certains somnifères augmenteraient le risque d'Alzheimer (étude)

PARIS, 9 septembre 2014 (AFP) - L'utilisation à long terme de certains somnifères ou médicaments contre l'anxiété de la famille des benzodiazépines pourrait augmenter sensiblement le risque de développer une maladie d'Alzheimer, selon une étude franco-canadienne publiée mercredi.

Pendant six ans, les chercheurs ont étudié 1.796 cas d'Alzheimer répertoriés dans un programme d'assurance médicale canadien et les ont comparés à plus de 7.000 personnes en bonne santé, de même âge et de même sexe.

Dans l'étude publiée sur le site du British Medical Journal thebmj.com, ils ont montré que la prise de benzodiazépines durant plus de trois mois était associée à un risque accru d'Alzheimer pouvant atteindre 51%.

L'association était notamment liée à la durée d'exposition et était plus importante en cas d'utilisation de benzodiazépines ayant une longue durée d'action.

Les auteurs de l'étude parmi lesquels des chercheurs de l'Inserm et de l'Université de Montréal soulignent que leurs résultats "renforcent la suspicion d'un lien direct possible" entre prise de benzodiazépines et la maladie d'Alzheimer, même si ce lien doit encore être confirmé.

Les benzodiazépines, notent-ils, constituent "incontestablement des outils précieux pour traiter des troubles de l'anxiété et des insomnies temporaires".

Mais ils ajoutent que les traitements devraient être de courte durée et "ne pas dépasser trois mois".

Les résultats de l'étude vont dans le sens des mises en garde lancées par les autorités sanitaires de plusieurs pays contre l'utilisation des benzodiazépines, notamment chez les personnes âgées, en raison d'effets secondaires d'ordre cognitif.
C'est le cas de la France où l'agence du médicament ANSM critiquait en janvier dernier des durées de traitement encore souvent trop longues, avec des patients prenant ces médicaments en continu pendant plusieurs années, malgré les risques neuro-psychiatriques, de chute ou de dépendance encourus.

Selon l'ANSM, 11,5 millions de Français ont consommé au moins une fois une benzodiazépine en 2012, dont 7 millions pour l'anxiété et 4,2 millions pour des troubles du sommeil.

Les consommateurs avaient en moyenne 56 ans et étaient, pour près des 2/3 des femmes. Un tiers des femmes de plus de 65 ans prenaient une benzodiazépine contre l'anxiété et près d'une sur cinq pour dormir.

Pour limiter l'utilisation des somnifères de la famille des

benzodiazépines qui n'ont qu'un "effet faible" sur le sommeil, la Haute Autorité de santé (HAS) a pour sa part préconisé en juillet dernier de réduire leur remboursement par la sécurité sociale de 65% actuellement à 15% à l'avenir.
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Annexes 4: Miscellaneous

1. **Quality of the studies (Newcastle-Ottawa)**

2. **Profiles of benzodiazepine consumption**

3. **Adjustment for comorbidities associated with benzodiazepines and Alzheimer's disease. (ICD-9 and medication codes)**

4. **Risk of Alzheimer's disease associated with benzodiazepine use, sensitivity analysis (BENZODEM2), variables assessed 6 to up to 10 years before diagnosis**

1. Quality of the studies (Newcastle-Ottawa), Part II

1.1. Quality criteria for case-control studies identified before BENZODEM and BENZODEM2

Newcastle-Ottawa criteria to assess quality of case-control studies	Fastbom *et al.*, 1998[10]	Lagnaoui *et al.*, 2002[7]	Lagnaoui *et al.*, 2009[6]	Wu *et al.*, 2009[5]	Wu *et al.*, 2011[8]	Gallacher *et al.*, 2011[9]
Selection						
1) Is the case definition adequate? a) yes, with independent validation ⋆ b) yes, *e.g.* record linkage or based on self reports c) no description	⋆	⋆	⋆	Record linkage	Record linkage	⋆
2) Representativeness of the cases a) consecutive or obviously representative series of cases ⋆ b) potential for selection biases or not stated	⋆	⋆	Lack of representativeness	⋆	⋆	Selection bias
3) Selection of Controls a) community controls ⋆ b) hospital controls c) no description	⋆	⋆	⋆	⋆	⋆	⋆
4) Definition of controls a) no history of disease (endpoint) ⋆ b) no description of source	⋆	⋆	⋆	⋆	⋆	⋆
Comparability (of cases and controls on the basis of the design or analysis)						
a) study controls for (select the most important factor: age) ⋆ b) study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor)⋆	⋆ Depression not considered	⋆ ⋆	⋆ Depression not considered	⋆ Educational level not considered	⋆ Educational level not considered	⋆ ⋆
Exposure						
1) Ascertainment of exposure a) secure record (*e.g.* surgical records) ⋆ b) structured interview where blind to case/control status ⋆ c) interview not blinded to case/control status d) written self report or medical record only e) no description	⋆	⋆	Medical record	Medical record	Medical record	No description
2) Same method of ascertainment for cases and controls a) yes ⋆ b) no	⋆	⋆	⋆	⋆	⋆	⋆
3) Non-response rate a) same rate for both groups ⋆ b) non respondents described c) rate different and no designation	No description	No description	No description	⋆	⋆	No description
Total ⋆/ 9	**7**	**8**	**5**	**6**	**6**	**6**

1.2. Quality criteria for cohort studies (Newcastle-Ottawa criteria) identified before BENZODEM and BENZODEM2

Newcastle-Ottawa criteria to assess quality of cohort studies	Fastbom *et al.*, 1998[10]	Gallacher *et al.*, 2011[9]
Selection		
1) Representativeness of the exposed cohort a) truly representative of the average (describe) in the community ⋆ b) somewhat representative of the average in the community ⋆ c) selected group of users *e.g.* nurses, volunteers d) no description of the derivation of the cohort	⋆	⋆
2) Selection of the non exposed cohort a) drawn from the same community as the exposed cohort ⋆ b) drawn from a different source c) no description of the derivation of the non exposed cohort	⋆	⋆
3) Ascertainment of exposure a) secure record (*e.g.* surgical records) ⋆ b) structured interview ⋆ c) written self report d) no description	⋆	No description
4) Demonstration that outcome of interest was not present at start of study a) yes ⋆ b) no	⋆	No
Comparability (of cohorts on the basis of the design or analysis)		
a) study controls for (select the most important factor: age) ⋆ b) study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor) ⋆	⋆ Depression not considered	⋆ ⋆
Outcome		
1) Assessment of outcome a) independent blind assessment ⋆ b) record linkage ⋆ c) self report d) no description	⋆	⋆
2) Was follow-up long enough for outcomes to occur a) yes (select an adequate follow-up period for outcome of interest) ⋆ b) no	No: 3 years	Yes: 22 years*
3) Adequacy of follow up of cohorts a) complete follow-up - all subjects accounted for ⋆ b) subjects lost to follow-up unlikely to introduce bias-small number lost ->% (select an adequate%) follow-up, or description provided of those lost) ⋆ c) follow-up rate <% (select an adequate%) and no description of those lost d) no statement	45% dead or lost? No description	≈40% No description
Total ⋆/9	**6**	**6**

1.3. Quality criteria (Newcastle-Ottawa criteria) for BENZODEM and BENZODEM2 case-control studies

Newcastle-Ottawa criteria to assess quality of case-control studies	Billioti de Gage *et al.*, 2012[149]	Billioti de Gage *et al.*, 2014[179]
Selection		
1) Is the case definition adequate? a) yes, with independent validation ⋆ b) yes, *e.g.* record linkage or based on self reports c) no description	⋆	Record linkage
2) Representativeness of the cases a) consecutive or obviously representative series of cases ⋆ b) potential for selection biases or not stated	⋆	⋆
3) Selection of Controls a) community controls ⋆ b) hospital controls c) no description	⋆	⋆
4) Definition of controls a) no history of disease (endpoint) ⋆ b) no description of source	⋆	⋆
Comparability (of cases and controls on the basis of the design or analysis)		
a) study controls for (select the most important factor: age) ⋆ b) study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor) ⋆	⋆ ⋆	⋆ Educational level not considered
Exposure		
1) Ascertainment of exposure a) secure record (*e.g.* surgical records) ⋆ b) structured interview where blind to case/control status ⋆ c) interview not blinded to case/control status d) written self report or medical record only e) no description	⋆	Medical record
2) Same method of ascertainment for cases and controls a) yes ⋆ b) no	⋆	⋆
3) Non-response rate a) same rate for both groups ⋆ b) non respondents described c) rate different and no designation	⋆	⋆
Total ⋆/ 9	**9**	**6**

1.4. Quality criteria (Newcastle-Ottawa criteria) for BENZODEM cohort study

Newcastle-Ottawa criteria to assess quality of cohort studies	**Billioti de Gage *et al.*, 2012[149]**
Selection	
1) Representativeness of the exposed cohort a) truly representative of the average (describe) in the community ⋆ b) somewhat representative of the average in the community ⋆ c) selected group of users *e.g.* nurses, volunteers d) no description of the derivation of the cohort	⋆
2) Selection of the non exposed cohort a) drawn from the same community as the exposed cohort ⋆ b) drawn from a different source c) no description of the derivation of the non exposed cohort	⋆
3) Ascertainment of exposure a) secure record (*e.g.* surgical records) ⋆ b) structured interview ⋆ c) written self report d) no description	⋆
4) Demonstration that outcome of interest was not present at start of study a) yes ⋆ b) no	⋆
Comparability (of cohorts on the basis of the design or analysis)	
a) study controls for (select the most important factor: age) ⋆ b) study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor) ⋆	⋆ ⋆
Outcome	
1) Assessment of outcome a) independent blind assessment ⋆ b) record linkage ⋆ c) self report d) no description	⋆
2) Was follow-up long enough for outcomes to occur a) yes (select an adequate follow-up period for outcome of interest) ⋆ b) no	Yes: 15 years ⋆
3) Adequacy of follow up of cohorts a) complete follow-up - all subjects accounted for ⋆ b) subjects lost to follow-up unlikely to introduce bias-small number lost ->% (select an adequate%) follow-up, or description provided of those lost) ⋆ c) follow-up rate <% (select an adequate%) and no description of those lost d) no statement	 No statement
Total ⋆/9	**8**

2. Profiles of benzodiazepine consumption, Part III

(1= use, 0= non-use, .=missing value, 2=end of follow-up or dementia)

Profil of Benzodiazepine use during follow-up (new users T5)									Number
T0	T3	T5	T8	T10	T13	T15	T17	T20	
0	0	1	.	1	1	1	0	0	1
0	0	1	.	1	1	2	2	2	1
0	0	1	.	1	2	2	2	2	2
0	0	1	0	0	.	0	2	2	1
0	0	1	0	0	0	0	0	0	2
0	0	1	0	0	0	0	0	2	3
0	0	1	0	0	0	0	1	2	1
0	0	1	0	0	0	1	2	2	1
0	0	1	0	0	0	2	2	2	6
0	0	1	0	0	1	2	2	2	1
0	0	1	0	0	2	2	2	2	4
0	0	1	0	1	1	0	1	0	1
0	0	1	0	1	1	1	.	0	1
0	0	1	0	1	1	1	1	1	1
0	0	1	0	1	1	1	1	2	1
0	0	1	0	1	1	2	2	2	2
0	0	1	0	1	2	2	2	2	1
0	0	1	0	2	2	2	2	2	3
0	0	1	1	.	.	0	2	2	1
0	0	1	1	.	.	1	0	0	1
0	0	1	1	.	1	1	1	0	1
0	0	1	1	0	.	0	2	2	1
0	0	1	1	0	0	0	0	0	1
0	0	1	1	0	0	0	0	2	1
0	0	1	1	0	0	1	1	2	1
0	0	1	1	0	0	2	2	2	1
0	0	1	1	0	1	0	2	2	1
0	0	1	1	0	1	1	1	2	1
0	0	1	1	0	1	2	2	2	1
0	0	1	1	0	2	2	2	2	1
0	0	1	1	1	.	.	1	1	1
0	0	1	1	1	.	1	2	2	2
0	0	1	1	1	0	0	0	1	1
0	0	1	1	1	0	2	2	2	1
0	0	1	1	1	1	.	1	2	1
0	0	1	1	1	1	0	2	2	1
0	0	1	1	1	1	1	0	2	2
0	0	1	1	1	1	1	1	1	2
0	0	1	1	1	1	1	1	2	1
0	0	1	1	1	1	1	2	2	2
0	0	1	1	1	1	2	2	2	3
0	0	1	1	1	2	2	2	2	5
0	0	1	1	2	2	2	2	2	8
0	0	1	2	2	2	2	2	2	19
TOTAL									95

3. Adjustment for comorbidities associated with benzodiazepines and Alzheimer's disease (ICD-9 and medication codes), Part IV

1. Psychiatric comorbidity	ICD-9 code for diagnosis	Medication codes
1.1 Anxiety disorders		
Anxiety states	300.0	
Phobic disorders	300.2	
Obsessive-compulsive disorders	300.3	
1.2 Depression		
Major depressive disorder single episode	296.2	
Major depressive disorder recurrent episode	296.3	
Dysthymic disorder	300.4	
Depressive disorders not elsewhere classified	311	
1.3 Sleep disorder		
Specific disorders of sleep of nonorganic origin	307.4	
	327.3	
	327.4	
Sleep disturbance	780.5	

2. Cardiovascular comorbidities	ICD-9 code for diagnosis	Medication codes
2.1 Hypertensions and its complications (diagnosis and tretments)		
Diagnosis		
Essential hypertension	401.x	
Hypertensive heart disease	402.x	
Hypertensive chronic kidney disease	403.x	
Hypertensive heart and chronic kidney disease	404-x	
Antihypertensive drugs		
Anti-hypertensive drugs		240800
Agonistes alpha-adrénergiques		240816
Vasodilatateurs à action directe		240820
Inhibiteurs du système rénine-angiotensine-aldostérone		240844
Autres antihypertenseurs		240892
2.2 Myocardial infarction (diagnosis)		
Acute	410.x	
Old	412.x	
2.3 Stroke (diagnosis)		
Intracerebral hemorrhage	431.x	
Other and unspecified intracranial hemorrhage	432.x	
Acute, but ill-defined, cerebrovascular disease	436.x	
Other and ill-defined cerebrovascular disease	437.x	
2.4 Hypercholesterolemia (diagnosis and treatment)		
Diagnosis (Hypercholesterolemia pure)	272.0	
Hypocholesterolemiant drugs		
Fibrate		240606
Statin		240608
2.5 Diabetes (diagnosis and treatments)		
Diagnosis	250.x	
Antidiabetic drugs		682020
Alpha-glucosidases inhibitors		682002
Biguanides		682004
Inhibiteurs de la dipeptidyl peptidase IV (DDP-4)		682005
Insulines		682008
Analogues du meglitinide		682016
Sulfonylurées		682020
Thiazolidinediones		682028
Other antidiabetics		682092
2.6 Platelet inhibitors or oral anticoagulants treatment		
Oral anticoagulants (excluding heparins)		201204
Platelet inhibitors		201218

3. Other comorbidity (Charlston)	ICD-9 code for diagnosis
3.1 Chronic pulmonary disease (diagnosis)	
Other chronic pulmonary heart disease	416.8
Chronic pulmonary heart disease unspecified	416.9
Chronic obstructive pulmonary disease and allied conditions	490 to 496
Coal worker's pneumococoniosis	500.x
Abestosis	501.x
Pneumoconiosis due to other silicea or silicates	502.x
Pneumoconiosis due to other inorganic dust	503.x
Pneumonopathiy due to inhalation of other dust	504.x
Pneumoconiosis, unspecified	505.x
Chronic respiratory conditions due o fumes and vapors	506.4
Chronic and other pulmonary manifestations due to radiations	508.1
Respiratory conditions due to unspecified external agent	508.8
3.2 Rheumatic disease (diagnosis)	
Giant cell arteritis	446.5
Systemic lupus erythematosus	710.0
Systemic sclerosis	710.1
Sicca syndrome	710.2
Dermatomyositis	710.3
Polymyositis	710.4
Rheumatoid arthritis	714.0
Felty's syndrome	714.1
Other rheumatoid arthritis with visceral or systemic inolvement	714.2
Other specified inflammatory polyarthropathies	714.8
Polymyalgia rheumatica	725.x
3.3 Peptic ulcer (diagnosis)	
Gastric ulcer	531.x
Duodenal ulcer	532.x
Pectic ulcer, site unspecified	533.x
Gastrojejunal ulcer	534.x
3.4 Hemiplegia or paraplegia	
Heriditary spastic paraplegia	334.1
Hemiplegia and hemiparesis	342.x
Infantil cerebral palsy	343.x
Quadriplegia and quadriparesis	344.0
Paraplegia	344.1
Diplegia of upper limbs	344.2
Monoplegia of lower limb	344.3
Monoplegia ofupper limb	344.4
Unspecified monoplegia	344.5
Cauda equina syndrome	344.6
Paralysis unspecified	344.9
3.5 Renal disease	
Chronic glomerulonephritis	582
Nephritis and nephropathy, not specified as acute or chronic	583.0 to 583.7
Chronic kidney disease	585.x
Renal failure, unspecified	586.x
Disorders resulting from impaired renal function	588.0
Organ or tissue replaced by transplant (kidney)	V42.0
Renal dialysis status	V45.1
Encounter for dialysis and dialysis catheter care	V56
3.6 Malignancy or metastatic solid tumor	
Malignant neoplasm of lip, oral cavity and pharynx	140 to 149
Malignant neoplasm of digestive organs and peritoneum	150 to 159
Malignant neoplasm of respiratory and intrathoracic organs	160 to165
Malignant neoplasm of bone, connective tissue, skin and breast	170 to 175
Kaposi's sarcoma	176
Malignant neoplasm of genitourinary organs	179 to 189
Malignant neoplasm of other and unspecified sites (excluding secondary	190 to 195.8
Malignant neoplasm of lymphatic and hematopoietic tissue	200 à 208
Neoplasm of uncertain behavior of other and unspecified sites and tissues (plasma cells)	238.6
3.7 Liver disease	
Viral hepatitis B with coma, chronic without mention of hepatitis delta	070.22
Viral hepatitis B with hepatic coma, chronic with hepatitis delta	070.23
Viral hepatitis B without mention of hepatic coma, chronic without mention of hepatitis delta	070.32
Viral hepatitis B without mention of hepatic coma, chronic with hepatitis delta	070.33
Other specified viral hepatitis with hepatic coma	070.44
Other specified viral hepatitis without mention of hepatic coma	070.54
Unspecified viral hepatitis with hepatic coma	070.6
Unspecified viral hepatitis without mention of hepatic coma	070.9
Acute and subacute necrosis of liver	570.x
Chronic liver disease and cirrhosis	571.x
Hepatitis unspecified	573.3
Hepatic infarction	573.4
Other specified disorders of liver	573.8
Unspecified disorder of liver	573.9
Esophageal varices with bleeding	V42.7
Esophageal varices without mention of bleeding	456.0
Esophageal varices in diseases classified elsewhere	456.1
Hepatic coma	456.2
Portal hypertension	572.2
Hepatorenal syndrome	572.3
Other sequelae of chronic liver disease	572.4
	572.8
2.8 AIDS/HIV	
Human immunodeficiency	042.x
	043.x
	044.x

4. Risk of Alzheimer's disease associated with benzodiazepine use, sensitivity analysis (BENZODEM2), variables assessed 6 to up to 10 years before diagnosis, Part IV

	Cases n=1796 (%)	Controls n=7184 (%)	Univariable odds ratio (95%CI)*	Multivariable odds ratio (95%CI)	
				Model 1*†	Model 2*‡
Benzodiazepine ever use:					
Non-users	969 (54.0)	4568 (63.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Users	827 (46.0)	2616 (36.4)	1.52 (1.37 to 1.69)	1.50 (1.35 to 1.68)	1.44 (1.28 to 1.61)
Benzodiazepine density exposure (number of prescribed daily doses):					
Non-users	969 (54.0)	4568 (63.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-90	234 (13.0)	999 (13.9)	1.12 (0.96 to1.32)	1.11 (0.94 to 1.30)	1.07 (0.91 to 1.26)
91-180	88 (4.9)	271 (3.8)	1.55 (1.20 to1.99)	1.56 (1.21 to 2.01)	1.53 (1.18 to 1.97)
>180	505 (28.1)	1346 (18.7)	1.82 (1.60 to2.07)	1.79 (1.58 to 2.04)	1.71 (1.50 to 1.95)
Benzodiazepine elimination half-life:					
Non-users	969 (54.0)	4568 (63.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Short half-life (<20h)	542 (30.2)	1826 (25.4)	1.43 (1.27 to1.61)	1.42 (1.25 to 1.60)	1.37 (1.21 to 1.55)
Long half-life (≥20h)	285 (15.9)	790 (11.0)	1.73 (1.48 to2.01)	1.69 (1.45 to 1.98)	1.59 (1.36 to 1.87)

*Matched for age, gender and follow-up length.

†Model 1: adjusted for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolaemia (diagnosis or treatment), comorbidity (diagnosis).

‡Model 2: Model 1 further adjusted for anxiety, depression and insomnia diagnosis.

5. Relationship between benzodiazepine use and dementia in non users of antidepressants, BENZODEM2 case-control study, Part IV

5.1. Number of subjects included in the analyses

Note: A stratum was compounded by one case and four controls in the main analysis. We evaluated in table below strata which could be included in the stratified analysis (i.e. concordant strata with at least one case and one control without use of antidepressants 5 to up to 10 years before Alzheimer's disease diagnosis) and the arising number of cases and controls.

	Case per stratum (N=)	**Control per stratum (N=)**	**Strata (N=)**	**Total cases (N=)**	**Total controls (N=)**	**Total cases and controls (N=)**
	0	1	10	0	10	10
	0	2	45	0	90	90
	0	3	165	0	495	495
	0	4	217	0	868	868
Total discordant	-	-	*437*	*0*	*1463 (excluded)*	*1463 (excluded)*
	1	1	27	27	27	54
	1	2	148	148	296	444
	1	3	511	511	1533	2044
	1	4	673	673	2692	3365
Total concordant	-	-	***1359***	***1359 (included)***	***4548 (included)***	***5907 (included)***

5.2. Results of the analysis stratified on non use of antidepressants 5 to up to 10 years before Alzheimer's disease diagnosis

	Cases	Controls	Univariable odds	Multivariable odds ratio (95%CI)	
	n=1359 (%)	n=4548 (%)	ratio (95%CI)*	Model 1*†	Model 2*‡
Benzodiazepines ever use:					
Non-users	796 (58.6)	3004 (66.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Users	563 (41.4)	1544 (34.4)	1.37 (1.21 to 1.56)	1.36 (1.20 to 1.55)	1.32 (1.15 to 1.51)
Benzodiazepines density exposure (number of prescribed daily doses):					
Non-users	796 (58.6)	3004 (66.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1-90	183 (13.5)	648 (14.2)	1.08 (0.90 to 1.30)	1.09 (0.90 to 1.31)	1.06 (0.88 to 1.28)
91-180	41 (3.0)	160 (3.5)	0.98 (0.69 to 1.39)	0.99 (0.69 to 1.40)	0.96 (0.67 to 1.36)
>180	339 (24.9)	736 (16.2)	1.71 (1.47 to 2.00)	1.69 (1.44 to 1.97)	1.62 (1.38 to 1.91)
Benzodiazepine elimination half-life:					
Non-users	796 (58.6)	3004 (66.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)
<20h	402 (29.6)	1118 (24.6)	1.35 (1.17 to 1.56)	1.35 (1.17 to 1.56)	1.31 (1.13 to 1.51)
≥20h	161 (11.8)	426 (9.3)	1.43 (1.17 to 1.74)	1.41 (1.15 to 1.73)	1.35 (1.10 to 1.66)

*Matched for age, gender and follow-up length.

†Model 1: adjustment for high blood pressure (diagnosis or treatment), myocardial infarction (diagnosis), stroke (diagnosis), platelet inhibitors or oral anticoagulant treatment, diabetes mellitus (diagnosis or treatment), hypercholesterolemia (diagnosis or treatment), comorbidity (diagnosis).

‡Model 2: Model 1 with supplementary adjustment for anxiety, depression and insomnia diagnosis.