Chapter 6

General Discussion

In the treatment of neuropsychiatric symptoms (NPSs) and cognitive impairment in people with dementia, psychotropic drugs such as antipsychotics, anxiolytics, hypnotics/sedatives, antidepressants, and anti-dementia drugs are commonly prescribed. Due to a lack of evidence regarding their effectiveness for NPSs and the presence of serious adverse effects,[1] they are often recommended as a second-line treatment option only after non-pharmacological interventions have failed or when the symptoms may cause harm to the patient or caregivers.[1–3] Despite the recommendations and warnings,[4–6] the use of psychotropic drugs in older people with dementia is still high,[7,8] and healthcare staff and caregivers paid more attention to the effects and less awareness of the side effects.[9–14] Therefore, the purpose of this thesis was to examine the longitudinal patterns of psychotropic drug prescriptions in Dutch older people with dementia in recent years. Specifically, this thesis investigated the patterns of prescriptions for five groups of psychotropic drugs in community-dwelling older people with new-onset dementia during a five-year follow-up, the patterns of psychotropic drug prescriptions and general practice consultations in community-dwelling older people with prevalent dementia during the first two years of the COVID-19 pandemic, and the patterns of psychotropic drug prescriptions in nursing home residents from 2003 to 2018. Furthermore, a systematic review was conducted to explore the likelihood of successful withdrawal from psychotropic drugs.

The present chapter offers a comprehensive summary and reflection of the main findings derived from our research, accompanied by a discussion of methodological considerations and recommendations for both clinical practice and future research.

Main findings and interpretation

To address the varying levels of dementia severity and care needs among community-dwelling older people and nursing home residents, as well as the differences in their respective caregiving and support teams, separate studies were conducted to examine the patterns of psychotropic drug prescriptions for these two groups of populations. Besides, the study designs differed. To investigate the patterns among community-dwelling older people, individuals with new-onset dementia were included and followed for five years. To examine the patterns among nursing home residents, individuals with prevalent dementia in different years were included and assessed. The prescription patterns observed in the community-dwelling older people study were more closely linked to the deterioration of dementia and prescribing behaviour among general practitioners, whereas the prescription patterns observed in the nursing home resident study were indicative of changes in prescribing behaviour among elderly care physicians.

Psychotropic drug prescription patterns among subpopulations of community-dwelling older people with dementia: a five-year follow-up study from the onset of disease (chapter 2)

Given that the routinely collected general practice data used in this study do not contain in-depth information that may impact the prescription of psychotropic drugs, including the severity of dementia and NPSs, we instead opted to recruit individuals who had recently been diagnosed with dementia and followed them longitudinally. We categorized the population into subgroups based on their registration status and deregistration reasons, namely: community-dwelling (CD) throughout follow-up group, ultimately admitted to nursing homes (NH) group, ultimately died (DIE) group, and ultimately deregistered for unclear reasons (DeR) group. These approaches allowed us to gain a more comprehensive understanding of prescription patterns in this population and to make the results more interpretable.

Antipsychotics and antidepressants were the most commonly prescribed psychotropic drugs for community-dwelling older people. After the onset of dementia, antipsychotics were prescribed more frequently in the NH (6.42%) and DIE (8.98%) groups, while antidepressants were more frequently in the CD group (7.67%). General practitioners prescribed more antipsychotics and antidepressants for all subpopulations during the course of dementia, but the increase in prescriptions before institutionalization or death was only found for antipsychotics. Older people in the NH group showed the greatest increase in both antipsychotics and antidepressants. The patterns of anxiolytic and hypnotic/sedative prescriptions were without clear increases or decreases in most subpopulations during the follow-up or before events. However, the DIE group had an increase in the pattern of hypnotics/sedatives. A significant increase in anti-dementia drugs was observed in the CD group. In the terminal stage of life, we observed an increase in hypnotics/sedatives and a decrease in anti-dementia drugs.

The observed increase in antipsychotics and antidepressants among all subpopulations following the onset of dementia is expected, as NPSs tend to increase with the progression of dementia. Similar patterns were reported in previous studies as well.[8,15] However, we cannot rule out the possibility that the rise in prescriptions is due to insufficient use of psychosocial interventions. The available resources for psychosocial interventions for dementia are not sufficient, especially in the communities, which may result in a reliance on psychotropic drugs.[16,17] Additionally, general practitioners and family caregivers may have positive attitudes towards the effect of the psychotropic drugs, which could also lead to over-prescription of psychotropic drugs.[9,11,13] Notably, the NH group showed the fastest and most substantial increases in both antipsychotics and antidepressants, suggesting that this subpopulation experienced more psychotic and depressive symptoms and faster dementia deterioration.[3] It is reported that the use of antipsychotics and greater deterioration in NPSs were associated with nursing home admission.[18,19] Besides, older people with dementia may experience more NPSs,

particularly psychotic symptoms, prior to institutionalisation, given the significant increase in antipsychotics before admission.

The subpopulation who ultimately deceased had more antipsychotic prescriptions at the initial stage of the dementia diagnosis, which increased further during the end stage of life. On one hand, the use of antipsychotics in older people with dementia is associated with a higher risk of mortality.[19–22] On the other hand, people may experience more NPSs or delirium at the terminal stage of life, which could result in more antipsychotic prescriptions.[3,23] The pattern of prescriptions for hypnotics/sedatives was similar to that of antipsychotics, with an increase observed during the follow-up and before death. Palliative sedation may be recommended for refractory problem behavior in patients with dementia during the terminal phase of life to alleviate their suffering, hence an increase in hypnotics/sedatives is expected.[24,25] A decline in anti-dementia drugs was observed before death, which aligns with a previous study that concluded the inappropriate use of anti-dementia drugs at the end of life.[26]

The increasing patterns in prescriptions for antipsychotics and antidepressants across all subpopulations during the course of dementia may alert general practitioners to reconsider their prescribing behaviors and try non-pharmacological intervention more frequently to avoid the over-prescription of psychotropic drugs. Although we lacked information to determine the appropriateness of the antipsychotic prescription during the terminal phase, the increase in antipsychotics at this stage should prompt general practitioners to be cautious when prescribing for terminally ill older people with dementia.

Patterns of psychotropic drug prescriptions and general practice consultations among community-dwelling older people with prevalent dementia during the first two years of the COVID-19 pandemic (chapter 3)

In addition to analysing patterns during regular times, we conducted a study to investigate the impact of the COVID-19 pandemic on psychotropic drug prescriptions and general practice consultations in community-dwelling older people with dementia. By simultaneously examining both the prescriptions and consultations, we gained greater confidence in interpreting whether the observed fluctuations in prescriptions were due to interruptions in healthcare services.

Patterns of psychotropic drug prescriptions during the first two years of the COVID-19 pandemic

The analysis of the first two years of the COVID-19 pandemic period, from week 9 in 2020 to week 52 in 2021, revealed notable patterns in psychotropic drug prescriptions. Overall, the prescription rates of psychotropic drugs in both the North and South were lower or similar during the first two years of the COVID-19 pandemic period compared with the pre-

pandemic period. The prescription rate differences varied from -10.2‰ to 0.1‰ in the North and from -3.2‰ to 0.4‰ in the South. Within the two-year period, six distinct phases were identified: the first wave of the pandemic, the first intermediate phase, the second wave of the pandemic which includes two phases, the second intermediate phase, and the third wave of the pandemic. The prescription rates of most psychotropic drugs in both regions in the first wave of the pandemic were comparable to those in the pre-pandemic period, which decreased in the first intermediate period and remained at either lower or similar levels in the subsequent phases.

In the first wave of the pandemic, the prescription rates of psychotropic drugs were stable in this study. In contrast, previous studies reported that older people with dementia experienced more NPSs and increase in use of psychotropic drugs in the early stage of the pandemic.[27–32] It is possible that community-dwelling older people in this study also experienced increased NPSs at the beginning of the pandemic. However, the increased demand for healthcare services caused by the rise in the number of COVID-19-infected patients, and the implementation of lockdown policies, could potentially result in disruptions or delays in the provision of treatments for dementia.[33–35] This assumption was supported by the observed decrease in consultation rates in phase 1 in the North. Besides, there is a likelihood of underestimating the actual requirement for treatment (such as psychotropic drugs) of NPSs during this period. This could be attributed to delayed health-seeking behaviours among older people and/or their caregivers when confronted with NPSs. Although remote consultations were utilised as a complementary approach, they did not work as well as face-to-face consultations, resulting in missed detection of some NPSs.[36] What is more, we did not see a rebound in psychotropic drug prescribing after the termination of the first lockdown, but rather a reduction in prescriptions in phase 2. One possible reason could be NPSs are fluctuating and transient, and tend to remit spontaneously.[37,38]

In the subsequent phases, including the second and the third waves of the pandemic, the prescription rates of psychotropic drug remained at lower or similar levels than in 2019. The two studies that focused on the long-term impacts of the pandemic on psychotropics reported an increase in antipsychotics in the majority of the study countries but decreases were observed in some countries as well, stability in antidepressants, and a decrease in anti-dementia drugs.[39,40] Similar factors such as the healthcare service strains, lockdown policies, delayed healthcare-seeking behaviours, and delayed treatments may still have a role in the long term. On the other hand, it could also be that older people with dememtia experienced less NPSs due to having smaller social circle.[41,42] The shrinking of social circle due to restrictions and lockdowns might make older people with dementia feel safe and less stressed, and experience fewer triggers of NPSs, which resulted in lower prescription rates.[42]

Patterns of general practice consultations during the first two years of the COVID-19 pandemic

During the first two years of the COVID-19 pandemic, the general practice consultations rates were higher than in the pre-pandemic period. The consultation rate differences were 38.5‰ in the North and 38.4‰ in the South. During the first wave of the pandemic, there was a decline in consultation rates in the North at the beginning, which gradually returned to pre-pandemic levels by the end of this phase. In contrast, the consultation rates in phase 1 in the south remained at a similar level as the corresponding weeks in 2019. During the first intermediate period, consultation rates in both regions exhibited a comparable level to the corresponding weeks in 2019. In the subsequent phases, the consultation rates were higher. The pandemic had the most significant impact on the percentage of home visits, which was severely interrupted. In the northern region, the percentage of home visits started to increase approximately 6 weeks after the outbreak of COVID-19 and reached a slightly lower level than the pre-pandemic phase in the middle of phase 2, remaining at this level thereafter. The percentage of telephone consultations in the north showed opposing patterns. The southern region showed similar patterns to the north in terms of home visits and telephone consultations.

The observed different patterns of consultation rates between the North and the South during the first wave of the pandemic could potentially be attributed to the directional spread of the COVID-19 virus in the Netherlands, i.e. from South to North. At the beginning of the COVID-19 pandemic, there were no infected cases in the north. The decrease in consultations during this period is more likely to be associated with the implementation of measures and the lockdown. Similar interruptions in healthcare services were reported in other studies.[43–46] In contrast, the consultation rates in the South did not decline after the outbreak of the pandemic, which can be attribute to the impact of both COVID-19 and the lockdown policy. The distinct short-term patterns of consultation rates in these two regions may reflect the conflicting behaviours of community-dwelling older people with dementia. While they may attempt to minimize healthcare service utilisations and contact with healthcare staff to reduce the risk of infection, they may also have urgent healthcare needs that require consultations.[47] In the subsequent two waves, consultation rates in both regions did not decline. Instead, the consultation rates in 2021 were higher than in 2019, which might be related to flu and COVID-19 vaccinations, or compensatory consultations.[48–52]

Additionally, the proportion of telephone consultations increased at the beginning, while home visits were severely interrupted, which was restored in phase 2. Similar patterns in shifts of different types of consultations were found in studies with a broader population.[43,53] The change in the proportion of different types of consultations reflected that general practitioner adjusted the consultation strategy quickly and switched to telephone consultations to meet patients' healthcare needs. Telephone consultations remained at a slightly higher level than

in 2019, indicating that some older people with dementia were able to participate in remote telephone consultations, either on their own or with the assistance of caregivers.[34,36] However, physical consultations remained the most commonly used type in both regions, and were also preferred by caregivers and general practitioners.[36,54] These patterns of consultations may indicate that older people's healthcare-seeking behaviours were resilient to the pandemic.

Psychotropic drug prescription patterns in Dutch nursing home residents with dementia (chapter 4)

Antipsychotics and antidepressants were the two most frequently prescribed psychotropic drugs in Dutch nursing home residents. We had a positive finding of antipsychotics prescribed by elderly care physicians for Dutch nursing home residents over the last 15 years, which declined from about 40% to 20%. Stable trends were observed in the prescriptions for anxiolytics, hypnotics/sedatives, and antidepressants, while anti-dementia drugs exhibited an upward trend. Furthermore, the prescription of overall psychotropic drugs declined, from 63% in 2003 to 40% in 2018. We observed that older people with advanced age and prolonged nursing home stays were associated with fewer psychotropic drug prescriptions. Conversely, more severe NPSs were linked to increased psychotropic drug prescriptions. Interestingly, dementia severity was only associated with anti-dementia drug prescriptions and not with other psychotropic drugs.

The decline in antipsychotic prescriptions was similar to the patterns in previous studies.[55–58] Besides, the decline complied with the warnings on its side effects and the guideline on problem behavior in dementia.[3,5,59] The Dutch Association of Elderly Care Physicians recommends trying non-pharmacological treatments first before initiating psychotropic drugs, and emphasises closely monitoring the effects and side effects after the prescription.[3] The antipsychotic prescribing practices of elderly care physicians are changing in an expected trend, aligned with the guideline. However, the patterns of antidepressants, anxiolytics, and hypnotics/sedatives were stable, without significant decrease. There was no consistent pattern of these three groups of psychotropic drugs in previous studies.[3,5,59] On one hand, the stable patterns of other psychotropic drugs might reflect no or minimal compensatory prescriptions of antipsychotics, which is positive. On the other hand, the stability in prescriptions might reflect fewer efforts in prescribing fewer or discontinuing prescriptions timely. The overall psychotropic drugs remained high, which might alert elderly care physicians to keep trying to prescribe fewer psychotropic drugs and discontinue unnecessary medications.

The proportion of older residents with anti-dementia prescriptions varied from 0.8% to 14.4% in this study, which was lower compared with other studies.[24] However, we observed an increase in anti-dementia prescriptions in nursing home residents. The access to anti-dementia drugs varied in Europe, and the percentage of patients treated with anti-dementia drugs in the Netherlands was lower than in many other European countries, like UK and Denmark.[61] The

Dutch College of General Practitioners' dementia guideline does not recommend the use of anti-dementia drugs because of the limited effects and side effects.[62] The Dutch Association of Elderly Care Physicians' problem behavior guideline concludes that memantine is ineffective.[3] Additionally, most of the population in this study had moderate to severe dementia, which could be another possible reason for the fewer anti-dementia prescriptions.[63] For the increase in anti-dementia drugs, we could not rule out the possibility that the increase may be impacted by the low percentage (0.8%) of anti-dementia drug prescriptions in the WAALBED-1 study in 2003.[64] On the other hand, the increase might reflect the change in physicians' prescribing behavior. However, we are not sure about the reasons.

Successful withdrawal of antipsychotics or anti-dementia drugs: trial completion (chapter 5)

In order to encourage physicians and general practitioners to taper off psychotropic drug prescriptions, we would suggest communicating the positive side of psychotropic drug withdrawal, in terms of trial completion. In this review, we introduced one straightforward, well-reported outcome, trial completion, to assess the success of psychotropic drug withdrawal trials. In order to compare with previous reviews and assess how trial completion complements previous reviews' results, we included the same trials as previous reviews, instead of including all eligible trials.

We found that the risk ratio of trial completion was 0.95 for antipsychotic withdrawal, and it was 0.94 for anti-dementia drug withdrawal. The antipsychotic withdrawal trials did not lead to a statistical or clinically meaningful increase in NPSs, with a mean difference of 2.33 in units of the Neuropsychiatric Inventory.[65] Withdrawal of anti-dementia drugs led to a statistically significant but clinically negligible decline in cognitive functioning, with a mean difference of -0.81 in the units of the Mini-Mental State Examination.[66]

Almost all people with dementia benefited from discontinuing antipsychotics. Of those who continued to take antipsychotics, 63 per 100 people completed the trial, three more than those in the withdrawal group. Thirty-seven people dropped out despite taking antipsychotic drugs. For these 37 people, discontinuation of antipsychotics might be a better choice since they did not benefit from antipsychotics. Ninety-seven per 100 people would benefit from discontinuation antipsychotics. The duration of the studies ranged from 1 to 12 months. The longer the follow-up period, the more often a recurrence of NPSs occurred in people with dementia.[38] Guidelines recommend an attempt to taper the prescription psychotropic drugs after 3 months.[67–69] So, we synthesised the results of studies in a clinically relevant period (≤ 3 months), 81 per 100 people in the withdrawal group complete the trial, and 85 per 100 people in the continuation group completed the trial. Irrespective of trial duration, the difference in risk of trial completion was very small. Our findings confirmed results of prior reviews that withdrawal of antipsychotics had little or no impact on NPSs or the risk of dropout.[70,71]

Similarly, people would benefit from anti-dementia drug withdrawal as well. Sixty-eight per 100 people who discontinued anti-dementia drugs completed the trial, 4 less than in the continuation group. When the study duration was limited to three months, 86 per 100 people completed the withdrawal of anti-dementia drugs. The risk difference remained the same, with 4 persons less than in the continuation group. The withdrawal of anti-dementia drugs did not lead to a clinically meaningful decline in cognitive function.[66]

Over 80% of people with dementia could successfully discontinue antipsychotics and anti-dementia drugs within a three-month timeframe, without negative impacts on NPSs and cognitive function. Using trial completion as an outcome provides positive information to physicians and patients about the withdrawal of psychotropic drugs. They may feel empowered to try discontinuation.

Methodological considerations

In **chapters 2**, **3**, and **4**, we explored the longitudinal patterns of psychotropic drug prescriptions for older people with dementia in Dutch long-term care practice over the recent years. The methods used in each chapter differed. In **chapters 2** and **3**, we used routinely collected general practice data, to study the patterns in community-dwelling older people with dementia, both during regular times and during the COVID-19 pandemic. In **chapter 4**, we used secondary data from nine previous studies to study the patterns in nursing home residents with prevalent dementia. In **chapter 5**, we conducted a systematic review to assess the success of withdrawal psychotropic drugs. In this section, we reflected on the advantages and disadvantages of the data sources and the methods we used.

Real-world data: routinely collected general practice data

Using real-world data in clinical research is becoming more and more popular, because of the increasing accessibility of real-world data, and advanced statistical and machine-learning techniques.[72] It is an efficient and cost-saving way to perform research. However, there are barriers to the application of real-world data, such as data quality, and interoperability between different datasets.[73] Routinely collected general practice data is one kind of real-world data. In the Netherlands, general practitioners register patients' diagnoses or symptoms using International Classification of Primary Care (ICPC) codes,[74] and medication prescriptions using the Anatomical Therapeutic Chemical (ATC) classification.[75] The standardized codes increased the quality of the routinely collected general practice data and made the linkage between dataset easy. But since the data was not collected for research purposes, data were episodic and limited.[73] There might be errors in registration as well. Selecting the accurate target population and pre-cleaning of routinely collected data are important steps to get reliable results.

Both **chapter 2** and **chapter 3** used routinely collected general practice data, but in different ways. In **chapter 2**, we defined our target population as older people with incident dementia due to lacking information about dementia severity. Recruiting people with newly diagnosed dementia could increase their homogeneity. The date of the first diagnosis of dementia was the index date. Recruited people were followed up for five-year since the index date, similar to a panel survey. The registered prescription data were a bit messy. For example, there were two prescriptions with the same start date but different end date, prescriptions with a period longer than 6 months but another prescription for the same psychotropic drug was prescribed regularly in the same period. Thus, we only focused on whether the patients had a psychotropic drug prescription in a given period (every three months) and ignored its frequency and duration. Although this method led to the omission of certain information, it also facilitated the creation of a tidy and reliable dataset. We chose three months as the period according to the Dutch Association of Elderly Care Physicians' guideline for problem behavior in people with dementia, which states that anxiolytics and hypnotics/sedatives should not be used for more than 4 weeks, and antipsychotics, antidepressants, and cholinesterase inhibitors should be tapered off gradually after 3 months.[3]

In **chapter 3**, we still used routinely collected general practice data to explore the patterns of psychotropic drug prescription during the first two years of the COVID-19 pandemic. We had access to data collected in 2019, 2020, and 2021. In this study, we selected dynamic weekly populations with prevalent dementia, instead of incident dementia. Our target population was all older adults who have been diagnosed with dementia, whether it is the first diagnosis or not. We had the same problem, a lack of information on dementia severity. Therefore, we selected the target population weekly according to the same inclusion and exclusion criteria. We assume these weekly populations were comparable. We extracted the number of prescriptions and consultations in that week for the corresponding weekly population, similar to a trend survey. Besides, we did logic checks to improve the reliability of the data.

Some limitations of routinely collected general practice data remained unsolved. Missed or delayed diagnoses of dementia exist in general practice. Only 20% to 50% of people with dementia are diagnosed in high-income countries.[76] For example, 62% and 60% of older people estimated to have dementia have a coded diagnosis of dementia in UK and USA respectively, and about 50% Dutch patients with dementia are registered as such with their general practitioners.[77–79] Therefore, the extent to which the study population is representative of the dementia population is unclear. In addition, people may have different severities of dementia when they were diagnosed, and the selection of prevalent and incident dementia could not fully address the absence of dementia severity information. Besides, some other important information was missing, such as types of dementia, the severity of NPSs, socioeconomic status, and the reason/indication for psychotropic drug prescription. Alzheimer's disease and vascular dementia are the only two types of dementia that have their

own unique ICPC codes.[80] Other types of dementia can only be registered as dementia.

Secondary data

In **chapter 4**, we used data from nine previous studies conducted from 2003 to 2018, similar to a trend survey. When using secondary data, it is important to make sure the data in different studies are comparable. All these studies collected data in Dutch nursing homes. But they were heterogeneous in many aspects. First, the nine studies comprised two cross-sectional studies, one cohort study, and six cluster-randomized controlled trials. We extracted the baseline data for the cohort study and cluster-randomized controlled trials. However, different types of studies may be susceptible to bias due to the willingness or reluctance of nursing homes to participate in the trials. Second, these studies were conducted in different nursing homes, which might have different care routines. Thus, in the logistic regression model, we used the nursing home variable as a random effect. Third, the questionnaires used to assess the severity of dementia and NPSs differed. We imputed the score of dementia severity in two studies. For the assessment of NPSs, we only used the severity, without frequency. Fourth, the study population might differ due to slightly different inclusion criteria. We adjusted for age, gender, length of nursing home stay, the severity of dementia, and the severity of NPSs in regression models.

Systematic review

Trial completion is a pivotal outcome in assessing the success of the psychotropic drug withdrawal trials

In this review, we introduced trial completion as an outcome. There are several advantages of trial completion. First, it can be measured without error. Second, it is recorded for all participants, which reduces the risk of bias due to attrition and related missing data. Third, no reporting bias because this information is almost always presented in flow charts. Fourth, it may encourage researchers and medical staff to pay more attention to and communicate the positive side of discontinuation of psychotropic drugs. The absolute number of trial completion is meaningful. For example, 81 per 100 people could discontinue antipsychotics without reuse during three months, and 86 per 100 people for anti-dementia drugs. These results may make the physicians and patients or their caregivers feel willing and confident to try the withdrawal of psychotropic drugs.

Duration of withdrawal trials, not the longer the better

The duration of follow-up periods for antipsychotic withdrawal trials varied between one and twelve months. However, the course of NPSs is highly individualized and may fluctuate, resulting in spontaneous remission or relapse.[37,38,81] As a consequence, patients may be more likely to resume taking psychotropic drugs during longer follow-up periods due to these

symptoms' fluctuations. Therefore, it is important not to conclude that the withdrawal trial has failed simply because the patient has been re-prescribed psychotropic drugs after six months or a year. The Dutch Association of Elderly Care Physicians' guideline for problem behavior in people with dementia suggests tapering off psychotropic drugs after three months at most.[3] In this review, we have used three months as the relevant clinical period for sensitivity analysis. The success rate of antipsychotic withdrawal increased from 60 out of 100 people in studies lasting one to twelve months, to 81 out of 100 people in studies lasting one to three months. Similarly, an increase in success rate was observed in anti-dementia drug withdrawal trials when the study period was limited to three months. Therefore, it is more meaningful to communicate the success of psychotropic drug withdrawal during a clinically relevant period than over longer durations.

Recommendations

Clinical practice

In general, we suggest that both general practitioners and elderly care physicians reconsider their prescribing practices for psychotropic drugs when addressing NPSs related to dementia. For community-dwelling older people with dementia, we observed an upward trend in the prescription of antipsychotics and antidepressants during the course of dementia, particularly among those who eventually moved to nursing homes. While NPSs may become more frequent or severe as dementia progresses, the rise in psychotropic drug prescriptions can also be attributed to inappropriate prescribing practices, such as long-term prescriptions or an excessive reliance on psychotropic drugs. For nursing home residents, although there was a considerable decrease in antipsychotic prescriptions in past years, the overall prescription of psychotropic drugs remained high. These patterns indicate a need for greater attention to non-pharmacological interventions in managing the NPSs of dementia for both general practitioners and elderly care physicians.

Furthermore, we recommend that healthcare professionals consider a comprehensive treatment approach for managing NPSs in older individuals, as it may help older people to live in the community for longer periods and delay institutionalisation. There was a significant increase in the prescription of antipsychotics before nursing home admission, which may be attributed to an exacerbation of NPSs, such as psychosis and agitation. Our findings suggest that antipsychotics may not be sufficient in treating these symptoms, since they were finally admitted to nursing homes. However, we did not have information on the use of non-pharmacological interventions, which limits our confidence in the conclusions.

Additionally, we recommend that general practitioners exercise caution when prescribing antipsychotics for older people with dementia during their terminal phase of life. We observed an increase in the prescriptions for both antipsychotics and hypnotics/sedatives before death.

The increase in hypnotics/sedatives was expected since the aim of treatment during the palliative phase is to provide comfort rather than to treat symptoms. Antipsychotics may also be used during this terminal phase to manage symptoms, such as agitation, delirium or nausea. However, we are not sure whether the increase in antipsychotics was appropriate or not. Consequently, we advise general practitioners to carefully assess patients' symptoms and care needs, ensuring that antipsychotic prescriptions are in the best interest of the terminally ill.

During the first two years of the COVID-19 pandemic, general practice consultations were only interrupted in the first wave and recovered to similar or higher levels in the following phases. Besides, we observed an increase in telephone consultations after the outbreak of the pandemic. These findings may suggest that general practitioners promptly adjusted their healthcare providing methods and acclimated to the new routine during the pandemic. Furthermore, there was no increase in the prescription rates of psychotropic drugs compared to 2019, raising questions about whether the similar or lower prescription rates were due to patients' delayed healthcare-seeking behavior or general practitioners' delayed treatments for NPSs, or possibly a reduced prevalence of these symptoms resulting from a smaller social circle during the pandemic. This finding may prompt general practitioners to prioritize close monitoring of NPSs during future pandemics.

The synthesis of psychotropic drug withdrawal trials showed that more than 80% of people were able to successfully discontinue antipsychotics and anti-dementia drugs in three months. This result may encourage healthcare professionals to closely monitor and regularly assess NPSs after prescribing psychotropic drug prescriptions, and to taper them off when possible.

To enhance the accuracy of research utilising routinely collected general practice data, we suggest the inclusion of indicators for psychotropic drug prescriptions, dementia severity, and NPSs severity in the electronic health system. Besides, only Alzheimer's disease and vascular dementia have their own unique ICPC codes.[80] We would recommend assigning codes for other types of dementia, since variations in psychotropic drug recommendations among different types of dementia may result in differences in the prevalence and patterns of psychotropic drug prescriptions.

Future research

Routinely collected data are typically not collected for research purposes and often lack information beyond basic demographic data, diagnoses, and medications. For dementia studies that plan to use electrical health data, there are strategies to obtain more accurate and reliable data. First, it is advantageous to establish a clear definition of the target population, whether it comprises individuals with prevalent dementia or incident dementia. To enhance the validity of the results, it is advisable to include an age- and gender-matched control group without dementia. This control group can instil greater confidence in researchers regarding

whether the observed changes in prescriptions or other outcomes can be attributed to dementia or are related to other age-related mental health or psychiatric disorders. Additionally, linking routinely collected data with other biobank datasets could be an option to get more information. A third approach is to generate new variables based on known variables, such as creating a frailty index based on age, gender, previous diagnoses, and medication use.[82] Lastly, due to the underdiagnosis of dementia in general practice, future study could delve into the attributes of individuals who exhibit symptoms of dementia but have not received a formal diagnosis. Such investigations would contribute to our understanding of whether the phenomenon of underdiagnosis introduces biased outcomes or occurs randomly.

To gain a better understanding of the patterns of psychotropic drug use, we recommend conducting comprehensive studies that encompass all types of psychotropic drugs. Such an approach could help identify cases of compensatory psychotropic drug usage. In the case of anxiolytics and hypnotics/sedatives, a limited number of studies have reported their patterns, while our own study found stable or ambiguous trends.

For the pattern of antidementia drugs during the course of dementia, studying cholinesterase inhibitors and memantine separately would be a better choice. Cholinesterase inhibitors are recommended for the treatment of mild to moderate Alzheimer's disease to slow down cognitive decline or for the treatment of NPSs associated with Parkinson's Disease Dementia or Lewy Body Dementia.[83] The Dutch dementia guideline recommends memantine for moderate to severe Alzheimer's disease to mitigate cognitive decline, but not for other types of dementia or for agitation in Alzheimer's disease.[83] The overall patterns of anti-dementia drug use may not reflect a switch from cholinesterase inhibitors to memantine or a combination of both drugs during the progression of dementia.

There are three levels of data about the use of psychotropic drugs: prescriptions, dispenses, and actual use. Patients' adherence to prescriptions may impact their purchase behavior or their decision to take the medication. As we transition from prescription data to dispense data and subsequently to actual usage data, the precision of information regarding psychotropic drug use improves. Nursing home residents' prescriptions are more likely to reflect the actual use of psychotropic drugs because they are taken care of by formal caregivers, which leads to higher adherence to prescriptions. However, community-dwelling older people with dementia often live alone or are taken care of by informal caregivers, and their adherence plays an important role in the accuracy of data about psychotropic drug use. Researchers should choose the type of data based on their study aims (prescribing or use of psychotropic drugs) and accessibility to the data to obtain more reliable results.

Overall Conclusion

The key lessons we learned from the Dutch long-term care practice are the following. First, in Dutch communities, the prescriptions of antipsychotics increased during the course of dementia, particularly before nursing home admission and death, whereas the prescription of antidepressants only increased during the disease trajectory. The demonstration of this increase might prompt general practitioners to reconsider their prescribing practices. Additionally, during the first two years of the COVID-19 pandemic, the rate of psychotropic drug prescriptions was lower but the rate of general practice consultations was higher among community-dwelling older people with dementia. The unanticipated decrease in rate of psychotropic drug prescriptions may suggest the importance of closely monitoring the neuropsychiatric symptoms experienced by this population during future pandemics. Such monitoring would provide valuable insights into interpreting the observed patterns of psychotropic drugs prescriptions. Third, in Dutch nursing homes, there was a considerable decrease in antipsychotic prescriptions in recent years, but the overall psychotropic drugs prescriptions remained high. Lastly, according to the synthesis of withdrawal trials, over 80% of older people with dementia could withdraw antipsychotics and anti-dementia drugs within a three-month timeframe. These findings highlight the possibility of discontinuing psychotropic medication in this population, a topic of great interest in dementia management. In conclusion, the findings of this thesis suggest that there is room for improvement in the treatment of NPSs with psychotropic drugs by both general practitioners (in the community) as well as in elderly care physicians (in nursing homes). Further research and clinical practice should pay more attention to the appropriate use of psychotropic drugs, the assessment of indicators for the prescriptions, tapering off the psychotropic drugs when possible, and applying effective non-pharmacological interventions.

Footnote: ChatGPT was used to assist with phrasing in the general discussion and Chapter 3.

References

1. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6
2. Azermai M, Petrovic M, Elseviers MM, Bourgeois J, Van Bortel LM, Vander Stichele RH. Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms. *Ageing Res Rev*. 2012;11(1):78-86. doi:10.1016/J.ARR.2011.07.002
3. Richtlijnen en praktijkvoering Probleemgedrag bij mensen met dementie|Guidelines and Practice for Problem behavior in people with dementia. https://www.verenso.nl/richtlijnen-en-praktijkvoering/richtlijnendatabase/probleemgedrag-bij-mensen-met-dementie. Accessed March 15, 2023.
4. Gallini A, Andrieu S, Donohue JM, Oumouhou N, Lapeyre-Mestre M, Gardette V. Trends in use of antipsychotics in elderly patients with dementia: Impact of national safety warnings. *Eur Neuropsychopharmacol*. 2014;24(1):95-104. doi:10.1016/j.euroneuro.2013.09.003
5. CHMP assessment report on conventional antipsychotics. Procedure under Article 5(3) of Regulation (EC) No 726/2004. https://www.ema.europa.eu/en/documents/report/chmp-assessment-report-conventional-antipsychotics-procedure-under-article-53-regulation-ec-no-726/2004_en.pdf. Published 2008. Accessed March 15, 2023.
6. Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC. Impact of FDA black box advisory on antipsychotic medication use. *Arch Intern Med*. 2010;170(1):96-103. doi:10.1001/archinternmed.2009.456
7. Janus SIM, Van Manen JG, Ijzerman MJ, Zuidema SU. Psychotropic drug prescriptions in Western European nursing homes. *Int Psychogeriatrics*. 2016;28(11):1775-1790. doi:10.1017/S1041610216001150
8. Joling KJ, Koppel M ten, van Hout HPJ, et al. Psychotropic drug prescription rates in primary care for people with dementia from recorded diagnosis onwards. *Int J Geriatr Psychiatry*. 2021;36(3):443-451. doi:10.1002/gps.5442
9. Cornegé-Blokland E, Kleijer BC, Hertogh CMPM, Van Marum RJ. Reasons to prescribe antipsychotics for the behavioral symptoms of dementia: A Survey in dutch nursing homes among physicians, nurses, and family caregivers. *J Am Med Dir Assoc*. 2012;13(1):80.e1-80.e6. doi:10.1016/j.jamda.2010.10.004
10. Lemay CA, Mazor KM, Field TS, et al. Knowledge of and perceived need for evidence-based education about antipsychotic medications among nursing home leadership and staff. *J Am Med Dir Assoc*. 2013;14(12):895-900. doi:10.1016/j.jamda.2013.08.009
11. Janus SIM, Van Manen JG, Ijzerman MJ, Bisseling M, Drossaert CHC, Zuidema SU. Determinants of the nurses' and nursing assistants' request for antipsychotics for people with dementia. *Int Psychogeriatrics*. 2017;29(3):475-484. doi:10.1017/S1041610216001897
12. Almutairi S, Masters K, Donyai P. The health professional experience of using antipsychotic medication for dementia in care homes: A study using grounded theory and focussing on inappropriate prescribing. *J Psychiatr Ment Health Nurs*. 2018;25(5-6):307-318. doi:10.1111/jpm.12464
13. Janus SIM, van Manen JG, Zuidema SU, Snijder C, Drossaert CHC, Ijzerman MJ. Reasons for (not) discontinuing antipsychotics in dementia. *Psychogeriatrics*. 2018;18(1):13-20. doi:10.1111/psyg.12280
14. Dhuny S, Foley T, Jennings A. General practitioners' knowledge of and attitudes towards prescribing psychoactive drugs in dementia care: a cross-sectional questionnaire study. *Ir J Med Sci*. 2021;190(2):667-675. doi:10.1007/s11845-020-02356-7
15. Orsel K, Taipale H, Tolppanen AM, et al. Psychotropic drugs use and psychotropic polypharmacy among persons with Alzheimer's disease. *Eur Neuropsychopharmacol*. 2018;28(11):1260-1269. doi:10.1016/j.euroneuro.2018.04.005
16. Jennings AA, Foley T, Mchugh S, Browne JP, Bradley CP. "Working away in that Grey Area.." A qualitative exploration of the challenges general practitioners experience when managing behavioural and psychological symptoms of dementia. *Age Ageing*. 2018;47(2):295-303. doi:10.1093/ageing/afx175
17. Jennings AA, Foley T, Walsh KA, Coffey A, Browne JP, Bradley CP. General practitioners' knowledge, attitudes, and experiences of managing behavioural and psychological symptoms of dementia: A mixed-methods systematic review. *Int J Geriatr Psychiatry*. 2018;33(9):1163-1176. doi:10.1002/GPS.4918
18. Brodaty H, Connors MH, Xu J, Woodward M, Ames D. Predictors of institutionalization in dementia: A three year longitudinal study. *J Alzheimer's Dis*. 2014;40(1):221-226. doi:10.3233/JAD-131850
19. Nerius M, Johnell K, Garcia-Ptacek S, Eriksdotter M, Haenisch B, Doblhammer G. The Impact of Antipsychotic Drugs on Long-term Care, Nursing Home Admission, and Death in Dementia Patients. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2018;73(10):1396-1402. doi:10.1093/gerona/glx239
20. Kheirbek RE, Fokar A, Little JT, et al. Association Between Antipsychotics and All-Cause Mortality Among Community-Dwelling Older Adults. *J Gerontol A Biol Sci Med Sci*. 2019;74(12):1916-1921. doi:10.1093/gerona/glz045
21. Schwertner E, Secnik J, Garcia-Ptacek S, et al. Antipsychotic Treatment Associated With Increased Mortality Risk in Patients With Dementia. A Registry-Based Observational Cohort Study. *J Am Med Dir Assoc*. 2019;20(3):323-329.e2. doi:10.1016/j.jamda.2018.12.019

22. Koponen M, Taipale H, Lavikainen P, et al. Risk of Mortality Associated with Antipsychotic Monotherapy and Polypharmacy Among Community-Dwelling Persons with Alzheimer's Disease. *J Alzheimers Dis*. 2017;56(1):107-118. doi:10.3233/JAD-160671
23. Addesi D, Maio R, Smirne N, et al. Prevalence of Delirium in a Population of Elderly Outpatients with Dementia: A Retrospective Study. *J Alzheimer's Dis*. 2018;61(1):251-257. doi:10.3233/JAD-170339
24. 2022 - Palliative sedation for refractory problem behavior in people with dementia. https://www.verenso.nl/richtlijnen-en-praktijkvoering/richtlijnendatabase/palliatieve-sedatie-bij-refractair-probleemgedrag-bij-mensen-met-dementie-handreiking. Accessed March 23, 2023.
25. Van Der Steen JT, Radbruch L, Hertogh CM, et al. White paper defining optimal palliative care in older people with dementia: A Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med*. 2014;28(3):197-209. doi:10.1177/0269216313493685
26. Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox Hayley D, Dale W. Integrating palliative medicine into the care of persons with advanced dementia: Identifying appropriate medication use. *J Am Geriatr Soc*. 2008;56(7):1306-1311. doi:10.1111/j.1532-5415.2008.01741.x
27. Cohen G, Russo MJ, Campos JA, Allegri RF. COVID-19 Epidemic in Argentina: Worsening of Behavioral Symptoms in Elderly Subjects With Dementia Living in the Community. *Front Psychiatry*. 2020;11:866. doi:10.3389/fpsyt.2020.00866
28. Aihara Y, Kiyoshi M. Depressive symptoms in community-dwelling older adults in Japan before and during the COVID-19 pandemic. *Int J Geriatr Psychiatry*. 2021;36(7):1122-1123. doi:10.1002/gps.5558
29. Moretti R, Caruso P, Giuffré M, Tiribelli C. Covid-19 lockdown effect on not institutionalized patients with dementia and caregivers. *Healthc*. 2021;9(7):893. doi:10.3390/healthcare9070893
30. Cagnin A, Di Lorenzo R, Marra C, et al. Behavioral and psychological effects of coronavirus disease-19 quarantine in patients with dementia. *Front Psychiatry*. 2020;11:1-15. doi:10.3389/fpsyt.2020.578015
31. Gedde MH, Husebo BS, Vahia I V., et al. Impact of COVID-19 restrictions on behavioural and psychological symptoms in home-dwelling people with dementia: A prospective cohort study (PAN.DEM). *BMJ Open*. 2022;12(1):50628. doi:10.1136/bmjopen-2021-050628
32. Lara B, Carnes A, Dakterzada F, Benitez I, Piñol-Ripoll G. Neuropsychiatric symptoms and quality of life in Spanish patients with Alzheimer's disease during the COVID-19 lockdown. *Eur J Neurol*. 2020;27(9):1744-1747. doi:10.1111/ene.14339
33. Brown EE, Kumar S, Rajji TK, Pollock BG, Mulsant BH. Anticipating and Mitigating the Impact of the COVID-19 Pandemic on Alzheimer's Disease and Related Dementias. *Am J Geriatr Psychiatry*. 2020;28(7):712-721. doi:10.1016/j.jagp.2020.04.010
34. Chirico I, Ottoboni G, Giebel C, et al. COVID-19 and community-based care services: Experiences of people living with dementia and their informal carers in Italy. *Heal Soc Care Community*. 2022;30(5):e3128-e3137. doi:10.1111/hsc.13758
35. Barry HE, Hughes CM. Managing medicines in the time of COVID-19: implications for community-dwelling people with dementia. *Int J Clin Pharm*. 2021;43(1):275-279. doi:10.1007/s11096-020-01116-y
36. Tuijt R, Rait G, Frost R, Wilcock J, Manthorpe J, Walters K. Remote primary care consultations for people living with dementia during the COVID-19 pandemic: Experiences of people living with dementia and their carers. *Br J Gen Pract*. 2021;71(709):E574-E582. doi:10.3399/BJGP.2020.1094
37. Vik-Mo AO, Giil LM, Ballard C, Aarsland D. Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study. *Int J Geriatr Psychiatry*. 2018;33(10):1361-1369. doi:10.1002/GPS.4933
38. Vik-Mo AO, Giil LM, Borda MG, Ballard C, Aarsland D. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. *Br J Psychiatry*. 2020;216(1):43-48. doi:10.1192/bjp.2019.195
39. Luo H, Lau WCY, Chai Y, et al. Rates of Antipsychotic Drug Prescribing Among People Living With Dementia During the COVID-19 Pandemic. *JAMA Psychiatry*. 2023;80(3):211-219. doi:10.1001/jamapsychiatry.2022.4448
40. Frazer JS, Frazer GR. Analysis of primary care prescription trends in England during the COVID-19 pandemic compared against a predictive model. *Fam Med Community Heal*. 2021;9(3):1143. doi:10.1136/fmch-2021-001143
41. Sabatini S, Bennett HQ, Martyr A, et al. Minimal Impact of COVID-19 Pandemic on the Mental Health and Wellbeing of People Living With Dementia: Analysis of Matched Longitudinal Data From the IDEAL Study. *Front Psychiatry*. 2022;13:849808. doi:10.3389/fpsyt.2022.849808
42. Talbot C V., Briggs P. 'Getting back to normality seems as big of a step as going into lockdown': the impact of the COVID-19 pandemic on people with early to middle stage dementia. *Age Ageing*. 2021;50(3):657-663. doi:10.1093/ageing/afab012
43. Tuppin P, Lesuffleur T, Constantinou P, et al. Underuse of primary healthcare in France during the COVID-19 epidemic in 2020 according to individual characteristics: a national observational study. *BMC Prim Care*. 2022;23(1):200. doi:10.1186/s12875-022-01792-x
44. Jones A, Maclagan LC, Schumacher C, et al. Impact of the COVID-19 Pandemic on Home Care Services Among Community-Dwelling Adults With Dementia. *J Am Med Dir Assoc*. 2021;22(11):2258-2262.e1. doi:10.1016/j.jamda.2021.08.031

45. Michalowsky B, Hoffmann W, Bohlken J, Kostev K. Effect of the COVID-19 lockdown on disease recognition and utilisation of healthcare services in the older population in Germany: A cross-sectional study. *Age Ageing*. 2021;50(2):317-325. doi:10.1093/ageing/afaa260
46. Schäfer I, Hansen H, Menzel A, et al. The effect of COVID-19 pandemic and lockdown on consultation numbers, consultation reasons and performed services in primary care: results of a longitudinal observational study. *BMC Fam Pract*. 2021;22(1). doi:10.1186/s12875-021-01471-3
47. Tuijt R, Rait G, Frost R, Wilcock J, Manthorpe J, Walters K. Remote primary care consultations for people living with dementia during the COVID-19 pandemic: Experiences of people living with dementia and their carers. *Br J Gen Pract*. 2021;71(709):E574-E582. doi:10.3399/BJGP.2020.1094
48. January 2021: Introduction of curfew and start of vaccination. https://www.rijksoverheid.nl/onderwerpen/coronavirus-tijdlijn/januari-2021-invoering-avondklok-en-start-vaccinatie. Accessed March 10, 2023.
49. Invitation letter for COVID-19 vaccination for people aged 85-89 years arriving today. https://www.rivm.nl/en/news/invitation-letter-for-covid-19-vaccination-for-people-aged-85-89-years-arriving-today. Accessed March 10, 2023.
50. Where and when to get the flu vaccine. https://www.rivm.nl/en/flu-and-flu-vaccine/where-and-when-to-get-the-flu-vaccine. Accessed March 10, 2023.
51. Repeat invitations for COVID-19 vaccination sent, people aged 60-64 can schedule GGD appointment as of today. https://www.rivm.nl/en/news/repeat-invitations-for-COVID-19-vaccination-sent. Accessed March 10, 2023.
52. Invitation for booster vaccination sent to people over 80. https://www.rivm.nl/en/news/invitation-for-booster-vaccination-sent-to-people-over-80. Accessed March 10, 2023.
53. Glazier RH, Green ME, Wu FC, Frymire E, Kopp A, Kiran T. Shifts in office and virtual primary care during the early COVID-19 pandemic in Ontario, Canada. *CMAJ*. 2021;193(6):E200-E210. doi:10.1503/CMAJ.202303
54. Due TD, Thorsen T, Andersen JH. Use of alternative consultation forms in Danish general practice in the initial phase of the COVID-19 pandemic – a qualitative study. *BMC Fam Pract*. 2021;22(1):108. doi:10.1186/s12875-021-01468-y
55. Selbæk G, Janus SIM, Bergh S, et al. Change in psychotropic drug use in Norwegian nursing homes between 2004 and 2011. *Int psychogeriatrics*. 2018;30(3):385-394. doi:10.1017/S1041610217001788
56. Pitkala KH, Juola AL, Hosia H, et al. Eight-Year Trends in the Use of Opioids, Other Analgesics, and Psychotropic Medications Among Institutionalized Older People in Finland. *J Am Med Dir Assoc*. 2015;16(11):973-978. doi:10.1016/J.JAMDA.2015.06.009
57. Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. *Lancet Public Heal*. 2017;2(3):e149-e156. doi:10.1016/S2468-2667(17)30031-2
58. Vasudev A, Shariff SZ, Liu K, et al. Trends in Psychotropic Dispensing among Older Adults with Dementia Living in Long-Term Care Facilities: 2004-2013. *Am J Geriatr Psychiatry*. 2015;23(12):1259-1269. doi:10.1016/j.jagp.2015.07.001
59. EMEA public statement on the safety of olanzapine (Zyprexa, Zyprexa Velotab). https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Pharmakovigilanz/Service/aktuelles/emea-zyprexa-st.pdf?__blob=publicationFile. Published 2004. Accessed March 20, 2023.
60. Lundby C, Jensen J, Larsen SP, Hoffmann H, Pottegård A, Reilev M. Use of medication among nursing home residents: A danish drug utilisation study. *Age Ageing*. 2020;49(5):814-820. doi:10.1093/ageing/afaa029
61. Europe A. European Dementia : Collaboration on First Interim Report. https://ec.europa.eu/health/ph_projects/2005/action1/docs/action1_2005_inter_10_en.pdf.
62. Group N working. NHG-Standaard Dementie (M21). https://richtlijnen.nhg.org/standaarden/dementie. Accessed March 20, 2023.
63. Ismail Z, Black SE, Camicioli R, et al. Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. *Alzheimers Dement*. 2020;16(8):1182-1195. doi:10.1002/ALZ.12105
64. Zuidema SU, Derksen E, Verhey FRJ, Koopmans RTCM. Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. *Int J Geriatr Psychiatry*. 2007;22(7):632-638. doi:10.1002/gps.1722
65. What is a clinically meaningful change in NPI score? https://npitest.net/faqs.html. Accessed April 20, 2023.
66. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimer's Dement Transl Res Clin Interv*. 2019;5:354-363. doi:10.1016/j.trci.2019.06.005
67. National Institute for Health and Care Excellence. Dementia: assessment, management and support for people living with dementia and their carers. *NICE Guidel*. 2018;(June 2018):2-43. www.nice.org.uk/guidance/ng97.
68. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association Practice Guideline on

the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia. *Am J Psychiatry*. 2016;173(5):543-546. doi:10.1176/appi.books.9780890426807

69. Zuidema SU, Smalbrugge M, Bil WME, Geelen R, Kok RM, Luijendijk HJ, van der Stelt I, van Strien AM, Vink MT, Vreeken HL. Multidisciplinary Guideline problem behaviour in dementia. Verenso, NIP. Utrecht 2018.
70. Pan YJ, Wu CS, Gau SSF, Chan HY, Banerjee S. Antipsychotic discontinuation in patients with dementia: A systematic review and meta-analysis of published randomized controlled studies. *Dement Geriatr Cogn Disord*. 2014;37(3-4):125-140. doi:10.1159/000355418
71. Van Leeuwen E, Petrovic M, van Driel ML, et al. Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia. *Cochrane Database Syst Rev*. 2018;3(3):CD007726. doi:10.1002/14651858.CD007726.pub3
72. Liu F, Demosthenes P. Real-world data: a brief review of the methods, applications, challenges and opportunities. *BMC Med Res Methodol*. 2022;22(1):1-10. doi:10.1186/s12874-022-01768-6
73. Swift B, Jain L, White C, et al. Innovation at the Intersection of Clinical Trials and Real-World Data Science to Advance Patient Care. *Clin Transl Sci*. 2018;11(5):450-460. doi:10.1111/cts.12559
74. Bentsen BG. International classification of primary care. *Scand J Prim Health Care*. 1986;4(1):43-50. doi:10.3109/02813438609013970
75. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC classification and DDD assignment, 2022. Oslo, 2021. https://www.whocc.no/atc_ddd_index_and_guidelines/guidelines/. Accessed May 31, 2022.
76. Alzheimer's disease A international. Dementia statistics | Alzheimer's Disease International (ADI). https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/. Accessed September 27, 2022.
77. Dementia | NHG Guidelines. https://richtlijnen.nhg.org/standaarden/dementie#volledige-tekst-richtlijnen-diagnostiek. Accessed September 19, 2022.
78. National Health Services (NHS). Recorded Dementia Diagnoses, June 2022 - NHS Digital. https://digital.nhs.uk/data-and-information/publications/statistical/recorded-dementia-diagnoses/june-2022. Accessed September 27, 2022.
79. Amjad H, Roth DL, Sheehan OC, Lyketsos CG, Wolff JL, Samus QM. Underdiagnosis of Dementia: an Observational Study of Patterns in Diagnosis and Awareness in US Older Adults. *J Gen Intern Med*. 2018;33(7):1131-1138. doi:10.1007/s11606-018-4377-y
80. ICPC-1 code finder | Based on NHG Table ICPC version 10. https://viewers.nhg.org/icpcviewer/?zoekstring=P70&geslacht=vrouw. Accessed March 24, 2023.
81. Eikelboom WS, van den Berg E, Singleton EH, et al. Neuropsychiatric and Cognitive Symptoms Across the Alzheimer Disease Clinical Spectrum. *Neurology*. 2021;97(13):e1276-e1287. doi:10.1212/WNL.0000000000012598
82. Drubbel I, De Wit NJ, Bleijenberg N, Eijkemans RJC, Schuurmans MJ, Numans ME. Prediction of adverse health outcomes in older people using a frailty index based on routine primary care data. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2013;68(3):301-308. doi:10.1093/gerona/gls161
83. Dementia. https://richtlijnendatabase.nl/richtlijn/dementie/behandeling_dementie/neurotransmitter-modulerende_geneesmiddelen/cholinesteraseremmers_bij_dementie.html. Accessed March 20, 2023.