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## The patterns in psychotropic drug prescriptions among older people with dementia

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## English Summary

Most older people with dementia experience neuropsychiatric symptoms (NPSs) during the trajectory of dementia. Psychotropic drugs should be used as a second-line treatment for NPSs when non-pharmaceutical treatments fail or when the symptoms threaten patients' or caregivers' safety. However, the prevalence of psychotropic drug prescriptions in older people with dementia is reported to be high, despite the availability of psychosocial interventions, guidelines, and publicity campaigns aimed at reducing the inappropriate use of psychotropic drugs. Thus, this thesis aims to investigate the patterns in psychotropic drug prescriptions among older people with dementia within the Dutch long-term care practice over the past decade. We estimated the patterns in psychotropic drug prescriptions in Dutch community-dwelling older people with dementia during the course of dementia (**Chapter 2**), and during the COVID-19 pandemic period (**Chapter 3**). We also explored the patterns in psychotropic drug prescriptions in nursing home residents with dementia (**Chapter 4**). We synthesised evidence for the success of withdrawing psychotropic drugs by introducing a new outcome variable, trial completion (**Chapter 5**).

**Chapter 2** explored the patterns of psychotropic drug prescriptions in different subpopulations of community-dwelling older people during a five-year follow-up after the onset of dementia using electronic health records (EHRs) from general practitioners in the northern region of the Netherlands. During the five-year follow-up, all subpopulations (the group who lived in the community throughout follow-up, the group who ultimately moved to nursing homes, the group who ultimately died, and the group who ultimately deregistered for unclear reasons) showed increases in prescriptions for antipsychotics and antidepressants. Besides, older people who were ultimately admitted to nursing homes showed the greatest increase in both antipsychotics and antidepressants. The patterns of anxiolytic and hypnotic/sedative prescriptions were without clear increase or decrease in most subpopulations. Additionally, before institutionalisation, only antipsychotics increased significantly. In the terminal stage of life, there was an increase in hypnotics/sedatives and a decrease in anti-dementia drugs.

**Chapter 3** investigated patterns in 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, comparing them to pre-pandemic patterns in 2019. EHRs from general practitioners were used. The results suggest that during the first wave of the pandemic, the prescription rates of most psychotropic drugs in both the north and the south were comparable to those in the pre-pandemic period. These rates decreased in the first intermediate period and remained either at lower or similar levels in the subsequent phases. The general practice consultation rates in the north and the south exhibited different patterns during the first wave of the pandemic. In the north, consultation rates initially declined but rebounded to the pre-pandemic level by the end of this phase. Conversely, consultation rates in

the south remained relatively stable, similar to the pre-pandemic period. In the first intermediate period, consultation rates in both regions were comparable to 2019. In the subsequent phases, there was an increase in consultation rates, possibly driven by factors such as the administration of flu and COVID-19 vaccinations. Notably, the proportion of home visits decreased after the pandemic outbreak but then restored in the middle of the first intermediate phase, although it remained slightly lower than the pre-pandemic levels in subsequent phases. In contrast, the proportion of telephone consultations showed an opposing pattern, initially increasing, then decreasing, but ultimately stabilising at a higher level than during the pre-pandemic period.

**Chapter 4** studied the patterns of psychotropic drug prescriptions in nursing home residents with dementia using secondary data from nine studies collected in Dutch nursing homes between 2003 and 2018. This study revealed a favorable pattern in antipsychotic prescriptions, which showed a notable decrease from approximately 40% to 20% from 2003 to 2018. The prescriptions of anxiolytics, hypnotics/sedatives, and antidepressants remained relatively stable. Conversely, there was an upward trajectory in anti-dementia drug prescriptions. Moreover, the overall psychotropic drug prescriptions declined from 63% in 2003 to 40% in 2018.

**Chapter 5** introduced a pivotal outcome variable, trial completion, to assess the success of withdrawing psychotropic drugs in people with dementia. In withdrawal trials of antipsychotics and anti-dementia drugs, no statistically significant difference was observed in the rates of trial completion between the withdrawal and continuous groups. Specifically, for antipsychotic withdrawal trials, the withdrawal groups exhibited a trial completion rate of 60 per 100 individuals, which was a modest decrease of 3 individuals compared to the continuation groups. In parallel, for anti-dementia drug withdrawal trials, the withdrawal groups demonstrated a trial completion rate of 68 per 100 individuals, indicating a slight reduction of 4 individuals in comparison to the continuation groups. Remarkably, over a span of three months, a substantial 81 out of 100 individuals successfully discontinued antipsychotics, while an even higher proportion, specifically 86 out of 100 individuals, managed to successfully discontinue anti-dementia drugs. Moreover, the withdrawal of antipsychotics did not result in severe NPSs. The withdrawal of anti-dementia drugs led to a statistically significant, yet clinically negligible, decline in cognitive functioning.

In the discussion section, we provide recommendations for clinical practice and offer suggestions for future studies based on the results of the studies. This thesis found an increase in prescriptions of antipsychotics and antidepressants in community-dwelling older people during the course of dementia, which may prompt general practitioners to reconsider their prescribing practices. Additionally, the unexpected decrease in the rate of psychotropic drug prescriptions during the first two years of the COVID-19 pandemic may reflect the neglect of NPSs during this period. Furthermore, in Dutch nursing homes, there has been a promising decline in antipsychotic prescriptions in recent years, although the prevalence of overall

psychotropic drug prescriptions has remained high. Finally, the synthesis of withdrawal trials indicates that over 80% of older people with dementia can withdraw antipsychotics and anti-dementia drugs within a three-month timeframe. In conclusion, the findings of this thesis suggest room for improvement in psychotropic drug prescribing practices of both general practitioners in communities and elderly care physicians in nursing homes. Further research and clinical practice should focus on the appropriate use of psychotropic drugs, the assessment of prescription indicators, the withdrawal of psychotropic drugs when feasible, and the application of effective non-pharmacological interventions.

## Nederlandse Samenvatting

De meeste oudere mensen met dementie ervaren neuropsychiatrische symptomen (NPSs) tijdens het beloop van hun ziekte. In de richtlijnen worden psychofarmaca als tweedelijns behandeling voorgeschreven, wanneer niet-medicamenteuze behandeling onvoldoende effectief is of wanneer de patiënt of zorgverleners in gevaar worden gebracht door de NPSs. Ondanks de beschikbaarheid van psychosociale interventies, richtlijnen en campagnes die zich richten op het verminderen van ongepast gebruik van psychofarmaca, worden er nog steeds veel psychofarmaca voorgeschreven bij oudere mensen met dementie. Dit proefschrift heeft daarom als doel om patronen te onderzoeken in het voorschrijven van psychofarmaca bij oudere mensen met dementie in de Nederlandse langdurige zorg over de afgelopen tien jaar. We hebben de patronen onderzocht in het voorschrijven van psychofarmaca bij Nederlandse thuiswonende oudere mensen met dementie tijdens het beloop van hun dementie (**Hoofdstuk 2**), en tijdens de periode van de COVID-19 pandemie (**Hoofdstuk 3**). We hebben ook de patronen onderzocht in het voorschrijven van psychofarmaca bij verpleeghuisbewoners met dementie (**Hoofdstuk 4**). In **hoofdstuk 5** hebben we door middel van een meta-analyse onderzocht of er wetenschappelijke bewijs is dat psychofarmaca succesvol afgebouwd kunnen worden. Daarvoor hebben we een nieuwe uitkomstmaat geïntroduceerd, namelijk het gerapporteerde aantal mensen dat een afbouwstudie volledig doorloopt, als proxy voor succesvol afbouwen.

In **hoofdstuk 2** hebben we patronen in het voorschrijven van psychofarmaca onderzocht bij verschillende subpopulaties van thuiswonende oudere mensen door middel van een nameting vijf jaar na het vaststellen van dementie op basis van elektronische patiëntendossiers (EPDs) van huisartspraktijken in Noord-Nederland. Bij alle subpopulaties (de groep die thuis woonde bij de nameting, de groep die uiteindelijk naar een verpleeghuis verhuisde, de groep die uiteindelijk overleed, en de groep die uiteindelijk was uitgeschreven vanwege onduidelijke redenen) was er een toename in antipsychotica en antidepressiva voorschriften bij de nameting na vijf jaar. De oudere mensen die uiteindelijk naar een verpleeghuis verhuisden hadden de grootste toename in antipsychotica en antidepressiva voorschriften. De patronen in anxiolytica en hypnotica/sedativa voorschriften lieten geen duidelijke toename of afname zien in de meeste subpopulaties. Alleen voordat iemand werd opgenomen in een verpleeghuis was er een significante toename in antipsychotica voorschriften. In de laatste fase van het leven werd er meer hypnotica of sedativa voorgeschreven en minder anti-dementie middelen.

In **hoofdstuk 3** hebben we de patronen in psychofarmaca voorschriften en huisartsconsulten onderzocht bij thuiswonende oudere mensen met vastgestelde dementie tijdens de eerste twee jaar van de pandemie, en dit vergeleken met pre-pandemische patronen in het aantal voorschriften in 2019. Dit is onderzocht door middel van elektronische patiëntendossiers (EPDs) van huisartspraktijken. De resultaten laten zien dat tijdens de eerste golf van de

pandemie, het aantal voorschriften van de meeste psychofarmaca in zowel het noorden als zuiden, gelijk waren aan de pre-pandemische periode. Het aantal voorschriften verminderde in de eerste tussenliggende periode en bleef laag of vergelijkbaar met het niveau in de volgende fases. Het aantal huisartsconsulten in het noorden en zuiden lieten verschillende patronen zien tijdens de eerste golf van de pandemie. In het noorden daalde het aantal consulten in eerste instantie, maar keerde het terug naar het pre-pandemische niveau aan het eind van deze fase. Daarentegen, bleef het aantal consulten in het zuiden relatief stabiel, en gelijk aan de periode voor de pandemie. In de eerste tussenliggende fase was het aantal consulten in beide regio's vergelijkbaar aan dat in 2019. In de volgende fases was er een toename in het aantal consulten, mogelijk door de administratie van koorts en COVID-19 vaccinaties. Met name het aantal huisbezoeken daalde na de pandemie, maar herstelde midden in de eerste tussenliggende fase. Echter bleef het aantal huisbezoeken iets lager dan het pre-pandemische niveau in de volgende fases. In het aantal telefonische consulten was het tegenovergestelde patroon te zien, eerst stijgend, daarna dalend, maar uiteindelijk stabiel op een hoger niveau dan in de pre-pandemische periode.

In **hoofdstuk 4** hebben we de patronen in het voorschrijven van psychofarmaca onderzocht bij verpleeghuisbewoners met dementie door middel van data die eerder is verzameld tijdens negen studies in Nederlandse verpleeghuizen tussen 2003 en 2018. Deze data liet een gunstig patroon zien in het voorschrijven van antipsychotica. Namelijk een afname van ongeveer 40% in 2003 naar 20% in 2018. Het voorschrijven van anxiolytica, hypnotica/sedativa en antidepressiva bleef relatief stabiel. Daarentegen, was er een opwaartse trend in anti-dementie middelen. Bovendien, was er een algemene daling in het aantal voorschriften van psychofarmaca van 63% in 2003 naar 40% in 2018.

In **hoofdstuk 5** hebben we door middel van een meta-analyse onderzocht of psychofarmaca succesvol afgebouwd kunnen worden. Daarvoor hebben we een nieuwe uitkomstmaat geïntroduceerd, namelijk het gerapporteerde aantal mensen dat een afbouwstudie volledig doorloopt, als proxy voor succesvol afbouwen. Bij het afbouwen van antipsychotica en antidementie middelen was er geen significant verschil in het aantal volledig afgeronde afbouwstudies tussen de afbouwgroep en de groep die de medicatie bleef gebruiken. Bij de antipsychotica afbouwstudies hadden 60 van de 100 personen in de afbouwgroep een volledig afgeronde afbouwstudie. Dit zijn 3 personen minder dan in de groep waarbij het middel gecontinueerd werd. Bij de afbouwstudies voor anti-dementie middelen, hadden 68 van de 100 personen in de afbouwgroep een volledig afgeronde afbouwstudie. Dit zijn 4 personen minder dan in de groep waar het middel gecontinueerd werd. Opvallend is dat over een periode van drie maanden, 81 van de 100 personen succesvol stopten met antipsychotica, terwijl een nog groter deel, namelijk 86 van de 100 personen succesvol stopten met anti-dementie middelen. Bovendien leidde het stoppen van antipsychotica niet tot ergere NPSs. Het afbouwen van anti-dementie middelen leidde tot een significante, maar in de praktijk verwaarloosbare, afname in

cognitief functioneren.

De discussie biedt aanbevelingen voor de praktijk en suggesties voor toekomstig onderzoek gebaseerd op de resultaten van de studies in dit proefschrift. Onze studies lieten een toename zien in antipsychotica en antidepressiva voorschriften bij thuiswonende oudere mensen tijdens het beloop van hun dementie. Dit kan huisartsen aansporen tot een heroverweging van hun voorschrijfbeleid. De onverwachte afname van psychofarmaca voorschriften tijdens de eerste twee jaar van de COVID-19 pandemie duidt mogelijk op het verminderd signaleren van neuropsychiatrische symptomen tijdens deze periode. Verder was er in Nederlandse verpleeghuizen een veelbelovende afname in antipsychotica voorschriften de afgelopen jaren, hoewel de prevalentie van het voorschrijven van psychofarmaca hoog is gebleven. De laatste studie toonde aan dat meer dan 80% van de oudere mensen met dementie hun antipsychotica en anti-dementie middelen succesvol kunnen afbouwen binnen een periode van 3 maanden. Concluderend laten de resultaten van dit proefschrift zien dat er ruimte is voor verbetering in het voorschrijven van psychofarmaca door zowel huisartsen als specialisten ouderengeneeskunde in verpleeghuizen. In verder onderzoek en in de praktijk zal er meer aandacht moeten worden besteed aan passend gebruik van psychofarmaca, het vaststellen van indicatoren voor het voorschrijven van psychofarmaca zoals NPS, het staken van psychofarmaca wanneer nodig, en de toepassing van effectieve niet-farmaceutische interventies.



## 中文总结

大多数老年痴呆症患者在疾病进展过程中都会经历精神行为症状。老年痴呆症患者的精神行为症状应首选非药物治疗，只有当非药物治疗无效，或精神行为症状威胁到患者自身和照顾者的安全时，才应考虑使用精神药物。当患者使用精神药物时，医务人员应密切监测患者对精神药物的反应和药物的副作用，及时停止使用精神药物。然而，尽管指南和社会宣传都倡导减少使用精神药物，既往研究显示，老年痴呆症患者中精神药物处方率仍然很高。因此，本论文拟探讨近几年荷兰社区居家和养老机构中老年痴呆症患者精神药物处方的变化趋势，为政策制定和临床实践改进提供理论依据。论文第二章研究了社区居家老年痴呆症患者自诊断痴呆症后的 5 年随访期间，其精神药物处方的变化趋势；第三章研究了 COVID-19 疫情爆发后的前 2 年，社区居家老年痴呆症患者的精神药物处方的变化趋势；第四章探讨了养老机构中老年痴呆症患者精神药物处方的变化趋势；第五章系统综述了停用精神药物处方的实验完成率。

第二章使用荷兰北部地区家庭医生注册数据，探讨了社区居家老人在确诊痴呆症后 5 年随访期间，不同亚组的精神药物处方模式。研究发现在 5 年随访期间，不同亚组（仍旧居住在社区组；最终入住养老机构组；在社区居住期间死亡组；和未知原因取消注册组）的抗精神病药和抗抑郁药处方不断增加。最终入住养老机构的老年人抗精神病药和抗抑郁药处方增速最快。多数亚组的抗焦虑药和安眠镇静药的处方模式没有明显变化。此外，在入住养老机构前 3 个月，只有抗精神病药处方量大幅增加。在生命终末期，安眠镇静药处方量增加，抗痴呆药处方量减少。

第三章也使用了家庭医生注册数据，研究 COVID-19 疫情前 2 年，社区居家老年痴呆症患者的精神药物处方和家庭医生咨询的模式，并将其与 2019 年疫情前的模式进行比较。研究结果显示，在第一波疫情期间，南部和北部两个地区的社区居家老年痴呆症患者的多数精神药物处方率与 2019 年同期比处于相似水平；在第一个间隔期（第一波疫情和第二波疫情之间的时期）有所下降；并在后续阶段稳定在和 2019 年同期相似或较低水平。疫情在荷兰的传播方向是由南向北，在第一波疫情爆发初期，荷兰北部地区受病毒感染的影响较小，因此南部和北部地区的全科就诊率在此阶段表现出不同的模式。北方地区老年痴呆症患者的家庭医生咨询数量在第一波疫情爆发后有所减少，但在第一波疫情结束时已反弹至和疫情前相似的水平。而南方地区老年痴呆症患者的家庭医生咨询数量在第一波疫情中保持稳定。自第二波疫情开始以来，南部和北部两个地区老年痴呆症患者的家庭医生咨询数量均有所增加，可能与流感疫苗和 COVID-19 疫苗接种有关。家庭医生咨询类型在疫情期间的变化包括，家访的比例在疫情爆发初期有所下降，在第一个间隔期有所恢复，但后续阶段仍略低于疫情前水平。相比之下，电话咨询的比例则呈现出相反的趋势，先上升后下降，但最终稳定在比疫情前较高的水平。

第四章使用 2003 年至 2018 年间在荷兰养老机构收集的 9 项既往研究的数据，分析荷兰养老机构中老年痴呆症患者精神药物处方的变化趋势。为了更准确的反应精神药物处方的趋势，本研究在分析精神药物处方的趋势时，根据患者痴呆症的严重程度和精神行为症状的严重程度对回归方程进行了调整。研究发现荷兰养老机构中老年痴呆症

患者抗精神病药呈现出可喜的下降趋势，从约 40% 降至 20%。抗痴呆药处方呈现显著增加的趋势。其他精神药物（抗抑郁药、抗焦虑药、安眠镇静药）未发现明显的变化趋势。此外，精神药物的总体处方量从 2003 年的 63% 下降至 2018 年的 40%。

第五章引入了一个新的结果变量，即实验完成率，以评估老年痴呆症患者停用精神药物实验的成功率。在临床实践中，老年痴呆症患者长期使用精神药物处方很常见。关注停药实验的完成率可以引导医生和患者关注积极的信息，更愿意在时机合适时尝试停用精神药物。在抗精神病药物和抗痴呆药物的停药试验中，停药组和持续用药组之间的试验完成率无显著差异。在抗精神病药物停药试验中，停药组每 100 人有 60 人成功停药，略低于持续用药组的实验完成率（少 3 人）。在抗痴呆药物停药试验中，停药组每 100 人有 68 人成功停药，比持续用药组的实验完成率低 4 人。值得注意的是，当我们将停药实验的时间段限定为三个月时，每 100 人中有 81 人成功停用了抗精神病药物，有 86 人成功停用了抗痴呆药物。此外，停用抗精神病药物并未导致严重的精神行为症状。而停用抗痴呆药物也未导致临床上显著的认知功能减退。

综上所述，该论文发现社区居家老年人确诊痴呆症后的随访期间，抗精神病药和抗抑郁药的处方量不断增加，该趋势可能会警醒全科医生反思其开具精神药物处方的行为，慎重开药。在 COVID-19 疫情的前两年，荷兰社区居家老人的精神药物处方率略有下降，可能反映出这一时期患者和 / 或医务人员对精神行为症状的忽视。在养老机构居住的老年痴呆症患者中，尽管总体精神药物处方率的仍然较高，但近年来抗精神病药物处方率出现了可喜的下降。此外，对停药试验的系统综述显示，超过 80% 的老年痴呆症患者可以在三个月内成功停用抗精神病药物和抗痴呆药物。本论文的研究结果表明社区全科医生和养老机构老年科医生的精神药物处方实践还有改进的空间。未来的研究和临床实践应重点关注以下主题：“精神药物的使用是否合理”，“评估并记录导致开具精神药物处方的症状”，“适时停用精神药物”，和“非药物干预措施的应用”。

## Acknowledgements

In my PhD journey, I've often found solace in a Chinese poem that seems to mirror my path: ‘山重水复疑无路，柳暗花明又一村.’ This verse captures the idea of persisting through challenges, ultimately discovering hope and unexpected beauty, a fitting summary of my PhD adventure.

I began my PhD journey in October 2018 with a focus on mental health rehabilitation for post-operative cardiac patients. However, progress in setting up the rehabilitation program and data collection was slower than anticipated, leaving me feeling somewhat out of control and stressed. Then, in late 2019, the COVID-19 pandemic disrupted our ability to collect data. Consequently, in March 2020, one and a half years into my PhD, I reached a pivotal moment when I decided to change my project towards dementia-related research, which aligned better with my research interests. Regaining control over the project was a wonderful feeling. I had the opportunity to delve into electronic health records, an incredible experience. During the last period of my PhD journey, I worked almost six days a week, often into the late hours, both on my thesis and in search of a postdoc position. It was exhausting, yet deeply fulfilling. Eventually, I completed my thesis on time and secured a postdoc position at the University of Oxford. It was a moment when all the hard work came to fruition.

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It is a bittersweet moment to say goodbye. While this chapter ends, the connections I've made with all of you wonderful people will remain a cherished part of my life. I eagerly anticipate the opportunity to reunite in the future!

## About the Author



Jiamin Du was born on 13<sup>th</sup> October, 1992, in Hebei, China. In September 2011, she was enrolled in the School of Nursing at Peking Union Medical College, where she earned a Bachelor of Science degree with a major in nursing in 2015. Subsequently, in September 2015, she began her master's program at Peking University, focusing her research on elderly care and the enhancement of the quality and efficiency of elderly caregiving in communities and nursing homes. She successfully obtained a Master of Science degree in 2018.

In October 2018, she commenced her PhD studies under the supervision of Prof. Sytse Zuidema and Dr. Sarah Janus at the Department of Primary and Long-term Care at the University of Groningen. During the PhD journey, her primary research goal has been to assess the patterns in psychotropic drug prescriptions among older people with dementia. She gained valuable experience in working with primary care electronic health records.

Since July 2023, she has been working as a postdoctoral researcher under the supervision of Prof. Vanessa Raymont, Prof. Clare Mackay, and Dr. Caroline Potter at the Department of Psychiatry at the University of Oxford. Her role involves evaluating the clinical benefits of the Oxford Brain Health Centre pathway in diagnosing and managing individuals with suspected memory disorders.

Jiamin's passion lies in contributing to the field of healthy ageing and enhancing the well-being of older adults.

## Publications

### *Publications during the PhD program:*

**Du J**, Janus SIM, de Boer M, Zuidema SU. The longitudinal patterns of psychotropic drug prescriptions for subpopulations of community-dwelling older people with dementia: electronic health records based retrospective study. *BMC Prim Care*. 2023;24(1):69. doi:10.1186/s12875-023-02021-9

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