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RESEARCH ARTICLE

Features of Polypharmacy in Dutch Older Outpatients with Personality Disorders: A Cross-Sectional Study

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Introduction: Pharmacotherapy in older adults with personality disorders (PDs) can be even more complicated compared to younger adults, because older adults stand at risk for polypharmacy and its negative consequences due to somatic comorbidities and biological age-related changes.

Aims: This study's primary objective serves to describe the point prevalence of polypharmacy in older adults with PDs. Next, we described 1) the number of psychotropics employed, 2) classes of psychotropics, 3) the number of somatic medication, and 4) the anticholinergic burden of the total medication.

Methods: This cross sectional study was performed at a clinical center of excellence for older adults with PDs in the Netherlands. Fifty outpatients aged 65 years and older with a primary diagnosis of a PD were selected from an alphabetically ordered list. Data from the files on polypharmacy (use of five medications or more daily), use of medication and the anticholinergic burden (ARS score) was collected.

Results: Polypharmacy was present in 72% of older adults with PDs. The mean number of psychotropics was 2.0 (SD = 1.4) psychotropics per person, for somatic medication the mean was 6.2 (SD = 3.6). Antidepressants were the most frequently prescribed (used by 62%), followed by anxiolytics (used by 40%). The mean ARS score was 1.1 points (SD = 1.7).

Conclusions: The prevalence of polypharmacy in older adults with PDs stands high, due to the high use of both psychotropics and somatic medication. Although this study provides important and new information on the use of medication in older adults, its representation of the population may be limited due to the tertiary care setting and small sample size excluding certain PDs (e.g., schizoid or obsessive-compulsive PD). Also, we did not register or measure the consequences of polypharmacy.

Keywords: polypharmacy, pharmacotherapy, anticholinergic burden, personality disorders, geriatric psychiatry

Case Study

Mrs. B., a 67-year-old woman known to suffer from lacunar stroke and hypertension, visited our Clinical Center of Excellence for Older Adults with Personality Disorders and was diagnosed with borderline personality disorder (BPD). She was voluntarily admitted to a psychiatric emergency department for older adults for 11 months because of suicidal ideations. Subsequently she was followed up at our outpatient clinic.

From the age of 25, she had an extensive history of recurrent depressions and anxiety disorders. Throughout the years, she was treated at various institutions and clinical wards, and thus received many psychiatric treatments prescribed by various psychiatrists. Treatments for depression consisted of pharmacotherapy, intensive group-therapy, and mindfulness. Treatment became more focused on pharmacotherapy, activation, and structuring daily life, as psychotherapy was not effective. Pharmacotherapy was mostly symptom-based, not always following existing guidelines. This could be due to the lack of continuity by the treating physicians, but also due to the high level of suffering that the patient expressed.

At the start of the 11-month admission, Mrs. B. was using eight medications. Nortriptyline 75 mg daily (plasma level of 96 ug/L) with mirtazapine 15 mg daily augmentation was indicated for the treatment of depression, while olanzapine 10 mg daily was prescribed off-label for insomnia. Amlodipine 5 mg daily, clopidogrel 75 mg daily, hydrochlorothiazide 25 mg daily and simvastatin 40 mg daily were prescribed for the treatment of hypertension and lacunar strokes and pantoprazole 40 mg daily was prescribed for stomach complaints. During the stay at our ward and outpatient follow up, several medications were changed by various psychiatrists and general practitioners for various indications. To treat depression, first lithium 400 mg (plasma level 0.58 mmol/L) was added. After three months the treatment was discontinued due to its inefficacy and the patient developing a tremor. Subsequently, nortriptyline was discontinued because of a prolonged QT interval (475 msec), which normalized after cessation (441 msec). Both were replaced by escitalopram 10 mg daily. Sometime around the start the patient developed a tinnitus. Tinnitus is reported as a possible side effect of escitalopram. The patient could not cope with tinnitus and developed suicidal thoughts. She was therefore no longer willing to use the escitalopram, but discontinuation did not improve the tinnitus. Escitalopram was then replaced by bupropion 150 mg daily. The patient became more active, but the subjective feeling of depressed mood did not improve. To treat mood instability and impulsivity related to BPD, valproic acid 1200 mg daily (plasma level 74 mg/L) was started. Several informants, such as practitioners and family, reported a positive influence on mood stability. The patient herself did not experience any improvement. For the treatment of insomnia, zopiclon 7.5 mg was prescribed. This did not have an effect, which is why it was replaced by temazepam 20 mg. Because of insufficient response, promethazine 25 mg was added (off-label). To treat anxiety, alprazolam 0.5 mg daily was added for a short period of time. To treat tension headache, diazepam 2 mg as well as fentanyl patches (50 ug/hour 1 patch every three days) were prescribed, the latter because of a spondylolisthesis as a result of falling. At the end of this period, Mrs. B. was using 14 medications daily.

She developed several somatic signs and symptoms that could be related to drug side effects: tremor (could be a side effect of lithium), prolonged QT interval (could be due to nortriptyline use), tinnitus (known side effect of escitalopram and amlodipine), weight gain (possibly related to olanzapine), sedation and falling incidents (both can be caused or worsened due to the sedative effects of psychotropics and the high anticholinergic burden of the total medication). At the outpatient clinic, pharmacotherapy was thoroughly evaluated by means of a medication review. Together with the pharmacist, indications for all the prescriptions were checked. After this, sedative medication (fentanyl, diazepam, alprazolam and promethazine) was tapered and discontinued. Mrs. B. became more active and less sedated.

Introduction

As the case description above illustrates, pharmacotherapy in older adults with personality disorders (PDs) can be complicated, which can easily lead to polypharmacy. Multiple definitions of polypharmacy exist in literature, but the most commonly used is the use of five or more drugs daily (regardless of ATC code) (Masnoon et al., 2017). Other used terms are excessive polypharmacy (use of 10 or more drugs daily) (Kann et al., 2015), psychiatric polypharmacy (use of 2 or more psychotropics daily) (Sarkar, 2017) and appropriate versus inappropriate polypharmacy (often using tools such as the Beers criteria to assess appropriateness) (Beers, 1997; Maggiore et al., 2010).

The prevalence of polypharmacy increases substantially with age and multimorbidity (Slabaugh et al., 2010). In the Netherlands, polypharmacy occurs in 44.3% of community dwelling older adults (aged 65 years and older) (Dijk et al., 2009). Over the last few decades, several studies have reported an increase in the use of prescription medication worldwide (Charlesworth et al., 2015; Nishtala & Salahudeen, 2015; Wastesson et al., 2016).

A recent review showed that, due to changes in pharmacodynamics, older adults are even more vulnerable to the consequences of polypharmacy (Kratz & Diefenbacher, 2019). Altered dopaminergic, serotonergic, and cholinergic systems can lead to an increased risk for extrapyramidal symptoms, agitation, urinary retention and even delirium (Kratz & Diefenbacher, 2019). Polypharmacy has also been associated with drug-drug interactions (Doan et al., 2013), adverse drug events (Bourgeois et al., 2010), falling (Fried et al., 2014), frailty (Gutiérrez-Valencia et al., 2018), mortality (Leelakanok et al., 2017) and cognitive impairment (Jyrkkä et al., 2011), including dementia (Park et al., 2017). Other potentially negative consequences of polypharmacy are the increased risk for potentially inappropriate medications (PIMs) (Tian et al., 2022) and increased anticholinergic burden, which means the cumulative drug effects of taking one or more drugs with anticholinergic properties (Tune, 2001; Mate et al., 2015). Use of drugs with high anticholinergic activity has been linked with cognitive impairment (Fox et al., 2014) and impaired physical functioning in older adults (Lampela et al., 2013).

In psychiatric populations, polypharmacy is a common issue; up to one-third of adult and older adult patients visiting an outpatient psychiatric department use three or more psychotropic drugs (Mojtabai & Olfson, 2010). In younger adults with PDs (six years after psychiatric admission), 10% of all patients use five or more medications daily (Zanarini et al., 2004). It is likely that older adults with PDs are exposed to even more polypharmacy, because they bear a higher risk of multimorbidity and they are more likely to use somatic medication (Slabaugh et al., 2010); however, due to the lack of research data, no exact percentages are known.

PDs are highly prevalent in older adults; rates of 10.6–14.5% in community dwelling older adults to 57.8% in nursing home residents are reported (Penders et al., 2020). Polypharmacy and its consequences may thus impact on healthcare facilities and the patients' quality of life (Montiel-Luque et al., 2017).

Medication reviews by a clinical pharmacist are an effective strategy to reduce inappropriate polypharmacy in older adults with mental disorders, reducing the total number of medications, PIMs, and potential drug-drug interactions (Stuhec & Lah, 2021). We performed a descriptive cross-sectional study in our tertiary outpatient clinic for PDs in older adults. This study's primary objective was to describe the point prevalence of polypharmacy in older adults with PDs. Next, we described 1) the number of psychotropics that were used, 2) classes of psychotropics, 3) the number of somatic medications and 4) the anticholinergic burden of the total medication.

Methods

Participants and Procedure

This study was performed in the month of May in 2017, in a Clinical Center of Excellence for Older Adults with Personality Disorders (tertiary care) at Heerlen, the Netherlands. We studied 50 consecutive patients from our outpatient department with a primary diagnosis of a PD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV (American Psychiatric Association, 1994), age 65 years or older. Comorbidity was allowed, as long as the primary diagnosis was a PD. It was estimated that fifty older adults with PDs would be enough to explore and give insight in the use of medication, which was the aim of this study. A patient case file study was carried out in fifty patient files of patients older than 65 years and with a primary PD diagnosis, obtained randomly from our population of older adults being treated for a PD at our outpatient clinical center. To obtain a sample that accurately represents our patient population and to avoid selection bias, patients were selected from an alphabetically ordered list of all patients receiving care at the Clinical Center of Excellence for

Older Adults with Personality Disorders at the time of inclusion. When 50 patients aged 65 years and older with a primary PD diagnosis were selected, the selection process was finished. For all participants, an informed consent to participate in scientific research was recorded in the patient files, as this is a standard procedure in our patient care process. We informed the participants that we would like to collect data on the use of medication to explore our treatment population. We informed the participants that their data would be anonymized and could not be tracked back to their personal data. They could agree or refuse, which was recorded in their file. We chose this design of consent because of the non-invasive and observational nature of this study. This study was not subject to the WMO (Dutch legislation for medical research in humans), because participants were not subjected to actions nor were behavioral rules imposed on them. It was therefore not obligatory to have it reviewed by a medical ethical committee. European General Data Protection Regulation (GDPR) only started in 2018, a year after this study took place.

Personality assessment was carried out using a standardized procedure based on the LEAD (Longitudinal, Expert, All Data) standard (Spitzer, 1983), which integrates information from the patient, informants, and additional psychological tests. These provisional PDs diagnoses were then discussed in a multidisciplinary team (psychiatrist, psychologist(s) and psychiatric nurse(s)) in order to reach consensus for a definite diagnosis of PD.

This was a cross-sectional study. The study follows the STROBE protocol for cross-sectional studies.

Measurements

Information on demographics (age and gender) and DSM-IV mental disorders at the date of the research assessment was extracted from 'mijnQuarant', an electronic health record. The electronic prescribing system of mijnQuarant contains the medication mentioned in the referral letter. When this information was unclear or no longer up to date, informed consent was asked from the treating physician to check the current medication use via contacting the patient's pharmacy. Polypharmacy was defined as the use of five medications or more daily, regardless of ATC3-code or dosage (Masnoon et al., 2017). Medication was categorized by indication into the subtypes of psychotropics or somatic medication. In case medication could be prescribed for both somatic and psychiatric indication (e.g., promethazine can be prescribed to treat allergy symptoms or to sedate in case of sleeping disorders or anxiety), we checked what the indication was, or if this information were not available, who prescribed the medication (e.g., a psychiatrist, which makes psychiatric indication more likely, or a general practitioner). Anticholinergic burden was assessed using the Anticholinergic Risk Scale (ARS) (Rudolph et al., 2008). The ARS is a ranked categorical list of commonly prescribed medications with anticholinergic potential, which predicts the risks of anticholinergic adverse effects at a given point in time. The ARS ranks medications for anticholinergic potential on a 3-point scale (0: no or low risk; 3: high anticholinergic potential). The ARS score reflects the total sum of points.

Data collection took place when the DSM IV's classification system was used in clinical practice in the Netherlands. All classifications are therefore recorded in DSM IV terms.

Statistical Analysis

We used descriptive statistics to describe the percentage or range, mean, and standard deviation (*SD*) of demographic variables, point prevalence of polypharmacy, use of psychotropics and somatic medication, and ARS score. Following a rule of thumb (Allende-Alonso et al., 2019), every group of PD would have to contain 30 patients to be able to detect differences between groups with statistical tests. We aimed to include only 50 patients in total, since the objective of this study was to explore and describe the use of medication, instead of testing. Therefore, no power analysis was performed.

Statistical analyses were performed using SPSS 19.0 for Windows.

Results

The mean age of the total study population was 73.2 years (ranging from 65 to 92 years) and 64% were female. Most patients (54%) were diagnosed as PD Not Otherwise Specified (NOS). Patients with paranoid, schizoid, schizotypal, histrionic or obsessive-compulsive PD were not included in this study. Polypharmacy was present in 72% of older adults with PDs and in 76.9% of older adults with BPD. Results are shown in Table 1.

Antidepressants were the most prescribed psychotropics in the total study population; 62% of included patients used antidepressants, followed by anxiolytics (used by 40%). Results were also reported for various types of PDs (Table 2).

The number of psychotropics in the total study population ranged between 0 and 6 prescriptions, with a mean of 2.0 (SD = 1.4) psychotropics per person.

The number of somatic medications in the total study population ranged between 0 and 14 prescriptions, with a mean of 6.2 (SD = 3.6) somatic medications per person (Figure 1).

In the total study population, the anticholinergic burden, represented by the ARS score, ranged from 0 to 6 points, with a mean of 1.1 points (SD = 1.7) (Figure 2). The BPD group showed the highest mean and the largest variation in

Table 1. Patient characteristics in a study sample of older adults with personality disorders

Characteristic	N = 50						
Sex, n (%)							
Males, <i>n</i> (%)	18	(36%)					
Females, n (%)	32	(64%)					
Age in years, M <i>(SD)</i>	73.2 <i>(6.4)</i>						
Subtype of personality disorder, n (%)							
Borderline	13	(26%)					
Narcissistic	2	(4%)					
Avoidant	4	(8%)					
Dependent	4	(8%)					
NOS	27	(54%)					
Polypharmacy, n (%)	36	(72%)					
Number of comorbid psychiatric disorders, M(SD)	0-4 2.0 <i>(0.9)</i>						
ARS score M(SD)	0-6	1.1 <i>(1.7</i>)					

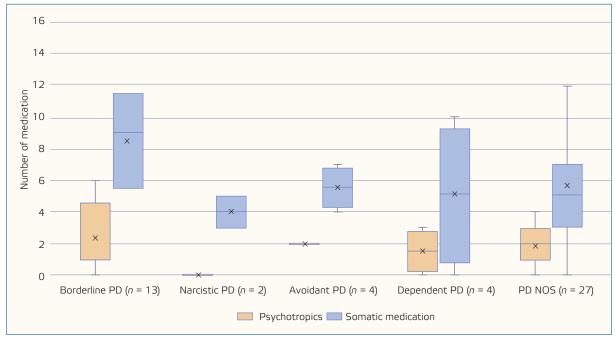
n= sample size, SD = standard deviation, PD = personality disorder, NOS = not otherwise specified, ARS = anticholinergic risk scale

Table 2. Use of various psychotropics for every group of personality disorder in older adults of the study sample

Variables	Total	Borderline	Narcissistic	Avoidant	Dependent	NOS
N(%)	50 (100%)	13 (26%)	2 (4%)	4 (8%)	4 (8%)	27 (54%)
Use of antipsychotics, n (%)	17 (34%)	4 (30.8%)	0	1 (25%)	1 (25%)	11 (40.7%)
Use of antidepressants, n (%)	31 (62%)	10 (76.9%)	0	4 (100%)	2 (50%)	15 (55.6%)
Use of mood stabilizers, n (%)	4 (8%)	1 (7.7%)	0	1 (25%)	0	2 (7.4%)
Use of anxiolytics, n (%)	20 (40%)	6 (46.2%)	0	2 (50%)	2 (50%)	10 (37%)
Use of sleep medication, n (%)	16 (32%)	6 (46.2)	0	0	0	10 (37%)

NOS = not otherwise specified, n = sample size

Figure 1. Distribution of data on use of medication amongst various groups of personality disorders in older adults of the study sample



PD = personality disorder, NOS = not otherwise specified, n = sample size

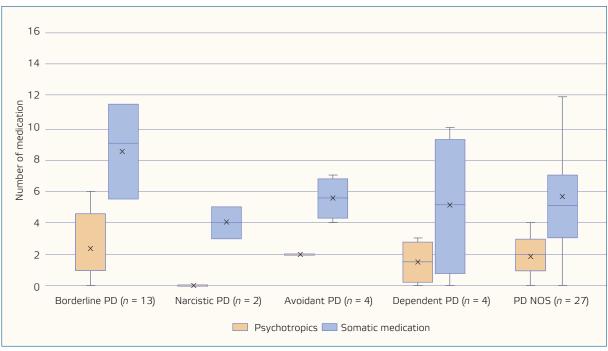


Figure 2. Distribution of the Anticholinergic Risk Scale-score, representing anticholinergic burden, amongst various groups of personality disorders in the study sample of older adults

ARS = anticholinergic risk scale, PD = personality disorder, NOS = not otherwise specified, n = sample size

ARS score, compared to the total group and compared to the other PD groups. However, no statistical tests were performed to test for significance.

Discussion

This study aimed to describe rates and features of polypharmacy, such as the use of psychotropics, use of somatic medication, and anticholinergic burden. To summarize, 72% of our sample including older adults with PDs had been exposed to polypharmacy. The mean number of psychotropics was 2.0 prescriptions per person, while the mean number of somatic medications was 6.2 prescriptions per person, and the mean anticholinergic burden in our study sample was 1.1 points.

In the Netherlands, 44.3% of community dwelling older adults use five or more medications daily (Dijk et al., 2009) and 20% use ten or more medications daily (Lemmens & Weda, 2015). In our study, focusing on a population of older adults with PDs, these numbers were even higher; 72% and 32%, respectively. The observed rate of polypharmacy in our study stands not only higher compared to community dwelling older adults, but also compared to younger adults with PDs, in whom rates of 10% have been reported (Zanarini et al., 2004).

There are some explanations for the high prevalence of polypharmacy in older adults with PDs. First of all, older adults with PDs, and older adults with mental disorders in general, are often excluded from randomized controlled trials. Due to this paucity of efficacy studies in older adults with PDs, treatment recommendations are based on studies with patients up to 50 years of age (American Psychiatric Association Practice Guidelines, 2001). Experts in treatment of PDs in older adults were consulted on their view on pharmacotherapy in older adults with PDs. They agreed that pharmacotherapy can be appropriate in older adults with PDs for the symptom based treatment of PDs, but the experts commented that psychiatrists have to rely on guidelines and studies which are aimed at younger to middle-aged adults with PDs, and therefore have to depend on their own knowledge, intuition, and clinical experience to translate recommendations to older adults (Schulkens et al., 2021). Lack of evidence-based recommendations may lead to an inappropriate prescribing and polypharmacy. Besides, somatic comorbidities are in general more prevalent in older adults compared to younger adults (Taylor et al., 2010), which can lead to a larger use of somatic medications, contributing to polypharmacy. Our data confirmed that the use of somatic medication constituted the most substantial component of polypharmacy in older patients with PDs, compared to the use of psychotropics. In line with our findings, in older adults having mental-physical multimorbidity living in geropsychiatric nursing homes, a

median number of seven somatic medications and a mean 2.3 psychotropics were reported per person (van den Brink et al., 2017). Although we did not investigate somatic comorbidities in our study, it is known that patients with PDs, and especially BPD, possess a significantly higher risk for somatic conditions, such as diabetes, hypertension, and osteoarthritis (Frankenburg & Zanarini, 2004). This can lead to multimorbidity, which is associated with polypharmacy (Slabaugh et al., 2010). This emphasizes the importance of monitoring somatic health in patients with PDs.

Older adults from this study population used two psychotropics on average, and were diagnosed with a mean of two comorbid psychiatric diagnoses. However, it is unlikely that psychotropics were prescribed only for these comorbid psychiatric disorders; having a PD seems to be a risk factor for polypharmacy, even more than other psychiatric diagnoses such as depression (Bender et al., 2001). Patients with PDs are more likely to be prescribed anxiolytics, mood stabilizers, antipsychotics, and antidepressants, compared to patients with a major depressive disorder (Bender et al., 2001). This can be related to the wide variety of symptoms being expressed in patients with PDs, which may lead to the prescription of several different psychotropics, e.g., antidepressants for depressed mood or anger, antipsychotics for suspiciousness and anxiety, etc. (American Psychiatric Association, 2001). Consequently, polypharmacy and psychotropic prescriptions can be the result of symptom-based prescribing, rather than the treatment of psychiatric comorbidity.

The anticholinergic burden in our study sample was on an average of 1.1 points, which remains higher compared to community dwelling older adults (mean ARS score 0.7 points) (Jun et al., 2020) or outpatients with dementia (mean ARS score of 0.31 points) (Watanabe et al., 2018). Antidepressants were the most commonly prescribed psychotropics in our study population. Tricyclic antidepressants, such as amitriptyline and nortriptyline, but also antidepressants such as mirtazapine and paroxetine impact the ARS score. Higher ARS scores have been associated with cognitive and physical impairment (Pasina et al., 2013) and anticholinergic adverse effects (such as falls, dry mouth, dizziness, and confusion) (Rudolph et al., 2008) in older adults. Older adults with PDs are therefore at risk for these adverse effects. Regular (at least yearly) medication reviews performed by psychiatrists and clinical pharmacologists should become routine in treating older adults with PDs, to reduce inappropriate polypharmacy, inappropriate prescriptions, and anticholinergic burden.

Based on our findings, there are some indications that the issue of polypharmacy is even more pronounced in older adults with BPD (point prevalence 76.9%) compared to the total study population. Predominantly, the use of somatic medication appears to be higher in older adults with BPD (mean 8.3 prescriptions, SD 4.3) compared to the total study population (mean 6.2, SD 3.6) resulting in a higher ARS score (mean 1.9 in BPD, compared to 1.1 in the total study population). This is, however, a preliminary finding that has not been tested for statistical significance due to the small size of the investigated population, but it calls for further research.

Strengths and Limitations

This study explores an important and understudied topic. Information on the use of medication in older adults with PDs is much needed. The population in which this study was conducted is very heterogeneous, due to complex comorbidity, which is possibly one of the reasons that these people are often not included in studies. However, it remains the population that visits many psychiatrists, making this study highly clinically relevant. This study's descriptive nature is appropriate to explore the use of medications.

However, this study also has several limitations. Firstly, this study was performed at a tertiary care clinic – which possibly induced some selection bias via selecting older adults with more complex and more severe PDs. This may have resulted in overestimating the prevalence of polypharmacy in older adults with PDs. Secondly, patients with paranoid, schizoid, schizotypal, histrionic or obsessive-compulsive PD had no representation in our sample, which may have decreased the study's external validity. Thirdly, the study was underpowered for detecting statistically significant differences among the various subtypes of PDs, because the groups were unequal in size. While the number of patients with narcissistic, avoidant, and dependent PDs remained small, there was an overrepresentation of PD not otherwise specified, similarly to the frequency observed in younger adult populations (Verheul & Widiger, 2004). In our study, this overrepresentation may also have been caused by the limited applicability of diagnostic tests and criteria to older adults, making them less likely to fulfill the diagnosis of a specific PD (Penders et al., 2020). For this reason, we presented descriptive statistics. Fourthly, we did not take into account possible consequences of polypharmacy, such as side effects or complications, which could have emphasized the importance of reducing polypharmacy. This will be an important focus in our future research.

Reflection on the Case of Mrs. B.

We experienced that the lack of guidelines for the treatment of PDs in older adults, a high level of suffering and help seeking behavior and the presence of a wide variety of symptoms were contributing to suboptimal pharmacotherapy. Mrs. B. was prescribed medication which are considered potentially inappropriate for people aged 65 years and older (TCAs) (Holt et al., 2010; Mann et al., 2023) and without proper indication (e.g., quetiapine for insomnia). However, when the treating psychiatrist and a clinical pharmacist performed a proper medication review, multiple medications (especially those with high anticholinergic burden) were tapered and discontinued, which led to an improvement in the patient's functioning and well-being.

Conclusion, Implications, and Future Directions

We conclude that the prevalence of polypharmacy in older adults with PDs was high due to the high use of both psychotropics and somatic medication. Polypharmacy is associated with adverse outcomes, such as falling, mortality and drug-drug interactions. Conducive to developing guidelines for a safer and more effective treatment, more research is essential. Research should focus more on older adults. The consequences of polypharmacy, such as side effects and complications, should be more appropriately investigated by means of empirical research. Similar research in the future should include larger sample sizes and investigate long-term effects in a prospective design. We think it is also important to include control groups in studies, such as younger to middle-aged adults with PDs and other older adults (e.g., without mental disorders). Treatment guidelines focusing on older adults with PDs should regard polypharmacy as an important risk in pharmacotherapy, and should include approaches to avoid polypharmacy, such as yearly systematical medication reviews.

Author contribution

Julie E. M. SHULKENS: conceptualization, design, methodology, investigation, project administration, data management, formal analysis, interpretation, writing original draft.

Sebastiaan P. J. van ALPHEN: conceptualization, design, methodology, interpretation, supervision, writing review and editing.

Frans R. J. VERHEY: conceptualization, interpretation, supervision, writing review and editing.

Sjacko SOBCZAK: investigation, design, methodology, formal analysis, interpretation, supervision, writing review and editing.

Declaration of interest statement

The authors declare no conflict of interest.

Ethical statement

This manuscript is the authors' original work.

All participants engaged in the research voluntarily and anonymously.

The participants provided their informed consent to participate in this study.

Their data are stored in coded materials and databases without personal data.

Data availability statement

Datasets presented in this article are available from the corresponding author upon reasonable request.

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