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SYSTEMATIC REVIEW

Factors Associated with Psychotropic Medication Use in People Living with Dementia in the Community: A Systematic Review and Meta-Analysis

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Abstract

Background There has been considerable focus on the use of psychotropic agents in people living with dementia in long-term care. However, psychotropic use often commences well before transitioning to long-term care.

Objectives To synthesize the available literature to identify factors associated with psychotropic medication use in people living with dementia in the community.

Methods This PROSPERO-registered review reports findings from a comprehensive search of Embase, PsycINFO, and PubMed (including MEDLINE) databases according to predefined inclusion and exclusion criteria (2010–2022). Inclusion criteria were original prospective or retrospective design research papers enrolling people diagnosed with dementia utilizing a psychotropic medication and living at home. Quality and risk of bias was assessed Newcastle–Ottawa Quality Assessment Scale. The last search was conducted in November 2022. Thematic analysis was used to synthesize the emergent factors identified, and a meta-analysis was undertaken on suitable data.

Results The search identified 619 articles. After review and exclusions, 39 articles were included for synthesis, including 1,338,737 people. The majority of papers (67%) were rated as low risk of bias and corresponding good quality. Thematic analysis suggested associations between psychotropic prescribing and patient and environmental factors, with little data concerning carer and prescriber factors. Such factors included age (< 75 years, > 90 years), sex, more advanced functional decline, and living alone. Meta-analysis identified significant associations between psychotropic use and respite (temporary full-time care or hospitalization) and comorbid psychiatric illness.

Conclusions While it is clear from this review that there remains a significant lack of clarity as to the reasons why these medications are being utilized in this population, this review provides greater insight and understanding into the context of psychotropic use. The study has highlighted an opportunity for further targeted research to be conducted and provides a much-needed context for this to occur.

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1 Introduction

Globally, the number of people living with dementia is predicted to increase from approximately 50 million in 2019 to 130 million in 2050 [1]. Approximately 60–70% of people with dementia live at home, while the remainder receives formal residential care of various types [2]. Given these exponentially increasing rates and rising healthcare costs, it is essential to understand how and what drives the management of this population's needs (physical, social, psychological, and behavioral) and whether resources and approaches are effective, appropriate, and cost efficient. This is all the more salient given the failings of aged care systems worldwide in meeting such needs [3–5].

Key Points

Psychotropic medication is utilized frequently for people with dementia living in the community.

Factors identified in this review provide opportunities for targeted intervention and further research.

Practical strategies for reflecting on psychotropic prescribing and optimizing psychotropic use are suggested.

Psychotropic medications, defined for the purpose of this paper as antipsychotics, antidepressants, anxiolytic/hypnotics (benzodiazepines and Z-drugs), anticonvulsants, and opioid medications, are frequently prescribed to people living with dementia [6]. Emerging literature has demonstrated that psychotropic prescribing in this population often begins in the community and is continued upon transition to long-term care, although the reasons for this are unclear [7].

Prevalence figures on psychotropic use in people living with dementia in the community range from 10 to over 50%, depending on the class of medication being used [8, 9]. These figures are alarmingly high given the burden of potential side effects and increased mortality risk associated with these medications in the absence of significant benefits [6, 10]. Hitherto, there has been extensive focus on psychotropic medication use in long-term care settings to implement quality measures and minimize inappropriate use in this setting [11–13]. However, there has been little comparative research into psychotropic medication use in people living with dementia in the community.

Critical work is being done in parallel to understand changed behaviors (also referred to as behavioral and psychological symptoms of dementia), the target symptoms for psychotropic treatment [14, 15]. Understanding the context of psychotropic use in this population is essential to improving their care and outcomes. By understanding the context of psychotropic use, further in-depth qualitative studies and targeted programs can be implemented to develop quality prescribing initiatives in this setting.

2 Objective

The primary objective of this systematic review and meta-analysis was to address the following research question: what factors (outcome) are associated with the use of psychotropic medication (intervention) in people living with dementia (population) in the community (context)?

3 Methods

3.1 Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used [16]. The review protocol was submitted to PROSPERO and published online in December 2021 (PROSPERO registration number: CRD42021286322).

An initial search of the Embase, PsycINFO, and PubMed (including MEDLINE) databases was conducted by two raters (KL and CP) in September 2021 using medical subject headings or free text (keywords) to reflect different indexing in databases. A final search was done in November 2022 for any new material. Nonpeer-reviewed literature, abstracts, gray literature, and opinion pieces were excluded because of the potential risk of bias and variable quality [17].

The search dates were January 2010 to November 2022, with 2010 chosen to avoid publications that focused on the effects of legislative changes concerning psychotropics and dementia, most of which occurred before 2009. The search strategy can be accessed in the supplementary material (S1).

Hand searches of the included publications' bibliographies were also conducted to identify additional relevant records. All search results were entered into EndNote version 20.2.1 (Clarivate, PA) to identify duplicates and organize material.

Inclusion criteria were retrospective or prospective research papers involving people living with dementia in the community using psychotropic medications, compared with people living with dementia in the community not using psychotropic medications. Exclusion criteria were reviews, commentaries, abstracts, and gray literature. Studies that only reported prevalence without associated factors or those primarily designed to investigate legislative changes in prescribing were excluded. Populations in which people with or without dementia were included, where subset analysis was not possible for the population with dementia only. Populations in which a transition from community living to full-time care occurred were included if the community-specific period could be evaluated separately. An English language criterion was applied for the first search; however, this was expanded to include all language papers, which did not identify any additional papers missed in the subsequent search. Papers involving opioid use were identified on the basis of a clear exclusion for opioid appropriate pain conditions. Two people (KL and CP) were involved in defining the search terms. The database search was conducted by one individual (KL) and the input of an experienced research librarian.

Two raters (KL and CP) independently reviewed papers and discussed all papers identified for exclusion. The first

round of reviews was conducted on the titles and abstracts. Any papers that were the subject of a disagreement between raters regarding exclusion were then reviewed in full in the next review round and discussed until a consensus was reached or the third reviewer (AW) provided adjudication. In the event of multiple reports relating to the same population and outcome, the most recently published report was selected. Data from the selected studies were extracted systematically into an Excel spreadsheet by KL. The data collected included generalized descriptive data, conceptual data subject to thematic analysis, and quantitative data for purposes of the meta-analysis. The data and spreadsheet were reviewed and independently verified by CP for accuracy.

3.2 Quality and Risk of Bias Assessment

Formal quality and risk of bias assessments were conducted independently by two researchers using a tool developed by Hoy et al. [18] for studies involving prevalence and the Newcastle–Ottawa Quality Assessment Scale for case-control and cohort studies [19]. A low risk of bias was indicated by the use of validated diagnostic criteria for dementia and consistent data input, such as mandatory population registries, clinical trials, or medical administration databases. Studies assessed as having a high risk of bias used less vigorous diagnostic criteria for dementia, used specific population groups, or had high dropout rates or poor comparability leading to less generalizability of results.

3.3 Data Synthesis and Analysis

Data from the selected studies were extracted systematically including country, sample size, participant demographics, diagnosis, objectives, outcome measures, quality, and bias rating.

Data were synthesized inductively, using thematic analysis to capture and interrogate data that were not amenable to meta-analysis. Thematic analysis is a validated and extensively utilized tool for the synthesis of data obtained from systematic reviews, particularly to synthesize data not amenable to meta-analyses. [20] A standard thematic analysis approach was adopted [20, 21]. Specifically, the reports/findings of all identified papers were examined and subjected to "free" or "open coding" whereby discrete concepts or patterns in relation to psychotropic prescribing were identified from the papers. These codes were then organized and grouped into "axial codes" by looking for similarities and differences between codes. Finally, higher order, abstract, or analytical themes were identified. This process was undertaken independently by a first coder (KL), followed by a second coder (CP), and then consensually.

Comprehensive Meta-Analysis Software version 2.2.027 (Biostat, NJ) was used to calculate raw data to event rates and pooled, adjusted event rates for different modifier subanalyses. Variables collected included psychotropic drug class, participant demographics, use of/no use of psychotropic medication by class, allowance for temporary respite care, and psychiatric comorbidity. A random-effects model was chosen over a fixed-effects model because the rates would likely vary between populations of different ethnicities, nationalities, and respite allowances with different mixes of psychiatric and dementia diagnoses, sex ratios, care levels, and health needs. Types of temporary respite accommodation outside the usual home were combined for analysis given the small numbers and overarching implications of any out of home care for psychotropic prescribing. In the event of missing data, we excluded the paper for meta-analytic purposes and therefore no extrapolation was included. Meta-analyses were based on separate psychotropic classes because it was not possible to cross-reference incidences of multiple or previous drug use, as most studies were cross-sectional and observational. Within-group heterogeneity was assessed using the I^2 statistic, and between-group heterogeneity was assessed using the Q-value statistic. Potential publication bias was assessed using Egger et al.'s regression intercept test [22]. Duval and Tweedie's trim and fill method was used to examine and impute possible missing samples [23]. Data were analyzed using IBM SPSS Statistics 25.0 for descriptive statistics, and forest plots were produced using Comprehensive Meta-Analysis Software. Relevant authors were contacted via email to obtain or augment data; however, the additional data obtained were insufficient for the purpose of inclusion in the meta-analysis.

4 Results

4.1 Search Findings

A PRISMA flow diagram of the study selection process is shown in Fig. 1. A total of 39 studies were included after inclusion and exclusion criteria were applied.

The study characteristics, key findings, and risk of bias are summarized in Table 1.

The sample size varied from 173 to 1,169,894, with a total sample size of 1,338,737 people living with dementia in the community. Of the studies, 17 included various analyses from a single population cohort, the Finnish Medication and Alzheimer's disease (MEDALZ) study database [24]. The MEDALZ study population was only counted once in the total subject sample of this review. However, each MEDALZ study cohort paper investigated a different outcome within

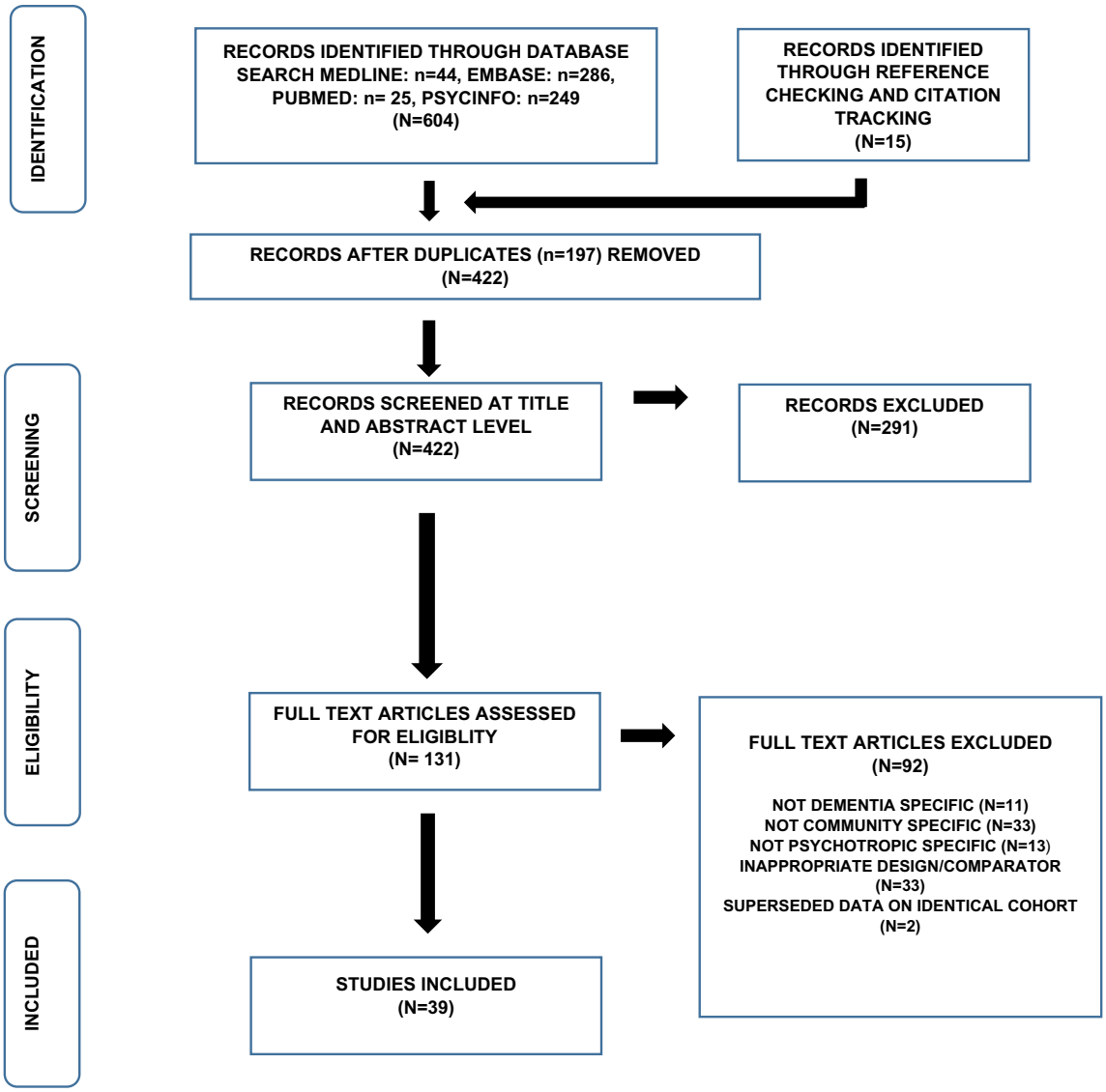

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram

this cohort and was included individually in the synthesis. Three large US studies based on Medicare administrative data were included; however, the population numbers were only included once to minimize the risk of over-inflation.

The country of origin of the studies included Finland ($n = 18$), the USA ($n = 11$), Canada ($n = 3$), Germany ($n = 2$), Italy ($n = 1$), Norway ($n = 1$), Sweden ($n = 1$), the Netherlands ($n = 1$), and France ($n = 1$). The participants' ages ranged from 37 to 100 years. One study specifically focused on people with younger onset dementia (ages < 65 years) [25], and one specifically on males [26].

The majority ($n = 26$; 67%) of the studies were rated as having a low risk of bias and corresponding good quality, and 13 (33%) studies were rated as having a moderate risk and fair quality. None were rated as having a high risk of bias or low quality. Agreement between independent assessors was high, with 90% agreement across the studies. All studies used quantitative or mixed methodologies. Five were prospective cohort studies, 29 were retrospective cohort studies, four were cross-sectional studies, and one was a nested case-control study.

4.2 Thematic Analysis and Synthesis

Following an inductive process and thematic analysis, factors common to the use of all psychotropic medications and factors associated with using specific classes of psychotropic medications were identified.

The thematic trends that emerged from the analysis are summarized for both psychotropic medications in general

Table 1 Study characteristics and bias rating ($n = 39$)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Aigbogun et al. (2020) [57]	489	Retrospective chart review Antipsychotics	Any type of dementia—mild, moderate, and severe	Not defined	Chronic psychotic conditions excluded Unspecified temp care	72.6 years (8.4)	48.5%	9.5 months mean duration of follow up from date of initiation of antipsychotic	85% of doctors did not measure behavioral symptoms formally. Most common reasons for prescribing antipsychotics included excessive motor activity and verbal aggression, physical aggression, anxiety, and irritability. 21.3% had nonpharmacological strategies documented prior to antipsychotic initiation. 9% were on two and 3.9% were on three different antipsychotic medications.	Moderate
Arbus et al. (2010) [33]	686	Prospective Cohort study Antidepressants	Mild–moderate Alzheimer's dementia	DSM IV/NINCDS-ADRDA	No exclusion for psychiatric diagnosis No respite care	77.9 years (6.8)	71.1%	Cross-sectional analysis at baseline	Antidepressant use associated with female gender and greater severity on Neuropsychiatric Inventory score (excluding depression item Antidepressant use associated with depression, anxiety, apathy, and aberrant motor behavior. 60% of those with depression were not treated.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Bargagli et al. (2019) [39]	24,735	Retrospective population-based cohort Antipsychotics	Any type of dementia	Hospital discharge records—diagnostic criteria not reported	Excluded people with schizophrenia or bipolar disorder No respite	> 65 years (no. mean/SD reported) 51.6% were 75–84 years	72.9%	Date of first antipsychotic prescription until end of study.	1727 new users of antipsychotics Antipsychotics more likely to be used in men and in those taking antidepressants and/or antidementia drugs. Typical antipsychotics more likely to be used in more rural locations and with lower socioeconomic status. 86% who stopped were re-initiated.	Moderate
Bhattacharjee et al. (2017) [34]	173	Retrospective cross-sectional study from the Medical Expenditure Panel Survey Data (2002–2012) Antidepressants	Any type of dementia with comorbid depression	ICD-9/or use of cholinesterase inhibitors as proxy for dementia	Depression diagnosis as an inclusion factor. No exclusion for psychiatric comorbidity. Unspecified temp care	> 65 years no. mean, or SD reported. 78.7% were > 75 years	69.7%	Two year follow-up	Prevalence of dementia and depression was 21.59%. 87.9% received some type of depression treatment. Antidepressants alone was associated with people > 75 years, while antidepressants and psychotherapy were combined in those aged 65–74 years. Use of any depression treatment declined with increasing age.	Low
Cermakova et al. (2017) [35]	26,163	Retrospective cohort study of Swedish Dementia Registry Antipsychotics Antidepressants Anxiolytic/hypnotics Opioids	Alzheimer's dementia/vascular dementia or mixed Alzheimer's and vascular dementia	ICD-10	No exclusion for psychiatric comorbidity No respite	80 years (no SD reported)	62%	Cross-sectional analysis study with data extraction at time of diagnosis and 1 year after	11,878 (46%) lived alone at the time of diagnosis. Living alone was associated with greater use of antidepressants, antipsychotics, and sedative/hypnotics. People who lived alone were more likely to be female, older, and have a slightly lower MMSE score.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Drummond et al. (2018) [36]	3252: (dementia no depression) 4262: (dementia no psychosis)	Retrospective cohort study Antipsychotics Antidepressants	Not specified	CPCSSN case definition of dementia	Exclusion of depression or psychosis as relevant in study design. No respite	82 year (8.2)	61.9%	Analysis from 6 months prior to diagnosis to 12 months following diagnosis	8.5% used an antidepressant without a diagnosis of depression. Antidepressant use associated with female gender, younger age, and prescription of anti-dementia medications. 6.1% used AP without diagnosis of psychosis. Antipsychotic use was associated with male gender, steroid use, and diagnosis of Parkinson's disease.	Moderate
Efjestad et al. (2021) [27]	11,764	Prospective study utilizing NorPD database from 2004 to 2016 Antipsychotics Antidepressants Anxiolytics/hypnotics Opioids	Alzheimer's dementia	Use of achei's as surrogate marker of diagnosis of dementia	No exclusion for psychiatric comorbidity No respite care	No mean or SD reported. Age range 37–88 years	63%	Analysis from four years prior initiation achei's to 2 years post-initiation	Female sex was associated with prescriptions of antidepressants, anxiolytics, opioids, benzodiazepines, and z-hypnotics. Male sex was associated with prescriptions of antipsychotics Polypharmacy was associated with female sex Sex associations were identified from 4 years prior to diagnosis	Moderate
Eichler et al. (2015) [52]	243	Cross-sectional analysis of randomized controlled intervention study (DelpHi-MV) Antipsychotics	Alzheimer's Dementia	DemTect < 9	Included psychiatric comorbidity No respite	79.6 years (5.4)	61%	12 month follow-up	Associations with antipsychotic use included having moderate cognitive impairment (defined in study as MMSE 10-19), functional impairment and treatment by a specialist.	Moderate

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Gerritsen et al. (2021) [25]	198	Longitudinal cohort study Antipsychotics Antidepressants Anxiolytics/hypnotics Antiepileptics	Alzheimer's disease, fronto-temporal dementia, vascular dementia, and mixed dementia	Mckhann criteria, NIND-AIREN criteria, FTD clinical consensus criteria.	Included psychiatric comorbidity Excluded known diagnosis of epilepsy No respite	60.9 years (5.5)	46.9%	2-year follow-up	Use of any psychotropic medication was associated with increasing age and apathy.	Low
Grace et al. (2016) [38]	598	Retrospective cross-sectional assessment of REACH II study data Antipsychotics, Antidepressants, Anxiolyitcs/hypnotics	Alzheimer's dementia	NINCDS criteria or MMSE< 23/30	No exclusion for psychiatric comorbidity No respite	79.06 year (9.26)	59%	Baseline analysis	Greater caregiver vigilance was associated with greater anxiolytic use. Greater caregiver confidence was associated with lower anxiolytic use Being white was associated with greater use of antipsychotics. Being younger and less cognitively impaired was associated with greater use of antidepressants.	Low
Grace et al. (2018) [46]	543	Retrospective cross-sectional analysis of REACH II data Antipsychotics Antidepressants Anxiolytics/hypnotics	Alzheimer's dementia	NINCDS criteria or MMSE < 23/30	No exclusion for psychiatric comorbidity No respite	77.84 years (10.26)	59.7%	Analysis of data at baseline assessment	Anxiolytics use was associated more frequently with African American racial groups relative to relative to non-Hispanic white racial groups. Antipsychotic use was associated more frequently with non-Hispanic white than Hispanic/Latino racial groups. There were no identified ethnic or racial differences in antidepressant use.	Moderate

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Hakala et al. (2021) [53]	22,357	Retrospective analysis of "MEDALZ" database Antipsychotics	Alzheimer's dementia	NINCDS-ADRA criteria or DSM-IV	Excluded psychiatric comorbidity No respite	81.6 years (No SD reported)	66.9%	Measurement at time of initiation of antipsychotic after 1 year washout	Hospitalization over 1 week or more was significantly associated with initiation of antipsychotic medication. Antipsychotic initiation was also associated with use of benzodiazepines and memantine. Older age (> 85 years) was associated with lower risk of antipsychotic initiation in association with hospitalization.	Low
Hamina et al. (2017) [32]	62,074	Retrospective analysis of "MEDALZ" database Opioids	Alzheimer's dementia	NINCDS-ADRA or DSM IV	History of substance abuse the only psychiatric exclusion Respite allowed < 90d ays	79.9 years (7.2)	67.1%	Analysis from time of diagnosis of dementia until end of study period (median follow up 1187 days, IQR 730–1766 days)	Prevalence of opioid use was 21.1% over the study period. Long-term use occurred in 7.2% of people with Alzheimer's disease. Long-term use was associated with older age (> 80 years), female gender, lower socioeconomic position, polypharmacy, rheumatoid arthritis, and long-term use of benzodiazepines.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Hamina et al. (2018) [56]	6654	Retrospective analysis of "MEDALZ" database Opioids Antipsychotics Benzodiazepine	Alzheimer's dementia	NINCDS-ADRA or DSM IV	No exclusion for psychiatric comorbidity Exclusion for > 6 month hospitalization prior to opioid initiation and < 10 days per month follow up due to hospitalization	82.2 years (no SD reported)	68.3%	Six months prior to opioid initiation until 6 months following opioid initiation in 30 day time intervals.	Antipsychotic use was 13.3% 6 month prior to opioid initiation, 18.3% at opioid initiation and 17.3% 6 month post opioid initiation. Benzodiazepine use was 27.1% 6 months prior to opioid initiation, 27.3% at opioid initiation and 26.9% 6 month after opioid initiation. Initiation of prescription opioids resulted in an immediate increase in both antipsychotic and benzodiazepine use, followed by a slight decrease in rate of new initiations of both antipsychotics and benzodiazepines over the following 6 months.	Low
Karttunen et al. (2019) [28]	69,353	Retrospective analysis of "MEDALZ" database Benzodiazepine Opioids	Alzheimer's dementia	NINCDR-ADRA or DSM IV	No exclusion for psychiatric comorbidity No exclusion on respite	80 years (7.1)	65.1%	Cumulative prevalence from 2005 to 2011. Median follow-up 1095 days	Factors associated with concomitant use of benzodiazepines and opioids were older age (> 80 ywars), female gender, low socioeconomic status, long-term benzodiazepine use (> 180 days continuous use), physical comorbidities (cardiovascular disease, asthma/chronic obstructive respiratory disease, rheumatoid arthritis, osteoporosis, active cancer, history of hip fracture, depression or bipolar disorder, and substance abuse history.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Kester et al. (2017) [40]	8688	Exploratory secondary data analysis of prospective Medical Administrative data Antipsychotics	Any dementia, enrolled in a Medicare Advantage Program	ICD-9	Diagnoses of schizophrenia or bipolar disorder were excluded Unspecified temp care	81.3 years (7.5)	68.6%	Period prevalence of data analyzed between November 2008 and January 2010	Factors associated with antipsychotic use included dual eligibility for Medicare and Medicaid, depression or substance use disorder, and older age. Female gender was associated with lower likelihood of antipsychotic prescription. People living in the Midwest or West were less likely to be prescribe antipsychotics.	Moderate
Koponen et al. (2015a) [61]	6740	Retrospective analysis of "MEDALZ" database Antipsychotics	Alzheimer's dementia	NINCDS-ADRA or DSM-IV	Excluded diagnosis of schizophrenia or bipolar illness Respite < 90 days	No mean or SD provided.	No cohort data reported.	7 year follow up starting 3 years prior to diagnosis of dementia until 4 years post diagnosis. (Long-term use defined as > 365 days)	2287/6740 (34%) used an antipsychotic medication. Median duration of first use was 219 days. Of those stopping, 44% restarted. Of first use, 39% lasted more than 1 year. Factors associated with long-term use include younger age (< 75 years). Older (> 85 years) females were more likely to initiate antipsychotics prior to diagnosis	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Koponen et al. (2015b) [44]	6087	Retrospective analysis of the "MEDALZ" database Antipsychotics	Alzheimer's dementia	NINCDS-ADRA or DSM-IV	Excluded chronic psychotic disorders and bipolar disorder Respite < 90 days	79.4 years (6.7)	63.8%	12 year follow-up following 2 year wash-out of prior antipsychotic use	Factors associated with antipsychotic initiation included use of benzodiazepines and antidepressants 71.5% of antipsychotic users, initiated at the time of diagnosis. People > 80 years and females initiated antipsychotics more frequently prior to diagnosis.	Low
Laitinen et al. (2011) [43]	28,089	Retrospective analysis of "MEDALZ" database Antipsychotics	Alzheimer's dementia	NINCDS-ADRA or DSM IV	No exclusion for psychiatric comorbidity No exclusion for respite	80 years (6.8)	67.8%	Annual prevalence of antipsychotic use during 2005.	6.6% had a history of psychosis recorded. Factors associated with antipsychotic use were female gender, polypharmacy, history of psychosis and diabetes, users of anti-dementia drugs, and differences according to university hospital district.	Low
Maust et al. (2020) [8]	737,839	Retrospective analysis of medical administrative database Opioids	Any type of dementia and Medicare beneficiar, > 65 years < 100 days in hospital or NH	ICD-9	No exclusion for psychiatric comorbidity < 100 days in hospital/respite allowance	82.2 years (SD not provided)	66.3%	1 year prevalence of psychotropic and opioid prescription fills	Factors associated with all psychotropic medications included female gender, younger age (65–74 years), non-Hispanic white race, and low-income groups. Rurality was associated with higher opioid use and lower antipsychotic use	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Maust et al. (2021) [50]	1,159,968	Retrospective analysis of Medicare claims database Antipsychotics Antidepressants Anxiolytics/hypnotics Opioids	Any type of dementia and traditional Medicare coverage between 2015 and 2017, < 100 days in hospital or NH	ICD-9 or DSM-IV	No exclusion for psychiatric comorbidity < 100 days hospital/respite allowance	Median age 83 years (IQR: 77.0–88.6 years),	65.2%	1 year prevalence of central nervous system active polypharmacy	71.2% of polypharmacy users were female. Factors associated with central nervous system active polypharmacy included: younger age (65–74 years), non-Hispanic white race, lower income groups, greater co-morbidities (excluding cancer) Polypharmacy users had greater incidence of noncancer pain, insomnia, psychiatric diagnoses, and seizure disorders. Antidepressants were associated most commonly with polypharmacy (92.1%)	Low
Nili et al. (2020) [41]	1,169,894	> 65 years, diagnosis of dementia, enrolled in traditional Medicare throughout calendar year Antipsychotics	Retrospective study of medical Administration database	ICD-9 or DMS-IV	Excluded psychiatric comorbidity No respite	No mean or SD reported. 61.9% were 80 years or older.	62.3%	Repeated cross-sectional study from 2006 to 2013	Older females less likely to use antipsychotic medications. Lower income had greater risk of using antipsychotic medications. Depression was positively associated with antipsychotic medication. Significant correlation between increasing Activities of Daily Living limitations and antipsychotic use. Residency in the mid-west also positively associated with antipsychotic use.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Orsel et al. (2018) [9]	70,719	Retrospective analysis of the MEDALZ database Antipsychotics Antidepressants Anxiolytics/Hypnotics Opioids	Alzheimer's disease, < 90 days hospital or full-time care	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 90 days	80.1 years (no SD reported)	65%	5 years prior to diagnosis to 4 years after diagnosis of AD. Point prevalence measured every 6 months	Psychotropic drug use was associated with female gender, asthma/COPD, hip fracture, stroke, psychiatric disorders, and any cardiovascular disease. Prior to diagnosis > 85 years more likely to use psychotropics, but after diagnosis, prevalence greater in those < 65 years. Psychotropic polypharmacy increased from 5.9% 5 years prior to diagnosis to 18.3% 4 years after diagnosis. Most common combination was an antidepressant and benzodiazepine. Factors associated with psychotropic polypharmacy were younger age (< 85 years), female gender and history of psychiatric illness.	Low
Puranen et al. (2017) [37]	62,104	Retrospective analysis of the "MEDALZ" database Antidepressants	Alzheimer's dementia	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 90 days	No mean or SD reported 50.1% > 80 years,	63.7%	Rate of new antidepressant use 9 years prior to diagnosis to 4 years after diagnosis, after 1 year washout of prior use.	Antidepressant use was associated with younger females. Greater percentage of initiations of antidepressants were written by geriatricians and neurologists. Highest incidence of antidepressant use at 6 months post diagnosis of 12.2 initiations per 100 person years.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Rhee et al. 2011 [48]	307	Retrospective analysis if ADAMS cohort between 2002 and 2004 Antipsychotics	Any type of dementia	DSM-IV	No exclusion for psychiatric comorbidity No respite	84.4 years (6.9)	68.3%	Cross-sectional analysis of baseline data	Associations with antipsychotic use included greater impairment in Activities of Daily Living, more severe dementia (based on CDR score), greater apathy and agitation scores, living alone, younger age, and diagnosis of Alzheimer's disease compared with vascular dementia Significantly less caregiver depression scores when patients were on antipsychotics. Less likely to be on antipsychotics if caregiver clinically depressed.	Low
Rios et al. 2017. [54]	40,650 (home care subset)	Retrospective analysis of the home care reporting system CIHI Antipsychotics	Any type of dementia	RAI-HC	No exclusion for psychiatric comorbidity No respite	84.3 years (7)	46.4%	One year prevalence in 2009 in Nova Scotia and in 2014 for other areas	Factors associated with antipsychotic use included wandering, anxious complaints, more severe cognitive impairment, use of antidepressants, psychiatric illness, and delirium. Antipsychotic use 19.2%, with 12% having no documented behavioral symptoms.	Moderate

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Saarelainen et al. (2015) [29]	70,718	Retrospective analysis of the 'MEDALZ' database Benzodiazepine	Alzheimer's dementia	NINCDR-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 90 days	79.1 years (range 34.1–104.6 years)	60.3%	Two years prior to dementia diagnosis to 3 years post diagnosis.	Factors associated with benzodiazepine use included female gender, history of psychiatric illness, higher Charleston Co-morbidity Index score, cardiovascular disease, hypothyroidisms, asthma, and chronic obstructive pulmonary disease.	Low
Sapra et al. (2012) [26]	407	Retrospective review of electronic medical records Antipsychotics	Any type of dementia, diagnosed between 2001 and 2009, enrolled in the Memory Disorders Clinic (MDC)	ICD-9	No exclusion for psychiatric comorbidity No respite	82 years (6.42)	0%	8 years.	Reasons for prescribing antipsychotics included agitation (60%), delusions (28.4%), hallucinations (21.6%), sleep disturbance (9.0%), and irritability (2.8%)	Moderate

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Sarycheva et al. (2018) [45]	70,718	Retrospective analysis of "MEDALZ" database Antiepileptics	Alzheimer's disease	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 90 day	Not reported for entire cohort.	Not reported for cohort	Follow-up commenced 9 years prior to diagnosis to 5 years post diagnosis.	4.3% of persons initiated an antiepileptic medication at the time of diagnosis of dementia, of whom only 34.9% had a diagnosis of epilepsy Factors associated with antiepileptic use include younger age, male gender, use of other psychotropic medications, concomitant psychiatric illness, and medical comorbidities. Prevalence of antiepileptic use increased to 7% by the end of follow-up. Incidence of epilepsy increased 2 years prior to diagnosis and peaked at 6 months post diagnosis. Men more likely to user older type antiepileptic medications together with antipsychotics	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Sivananthan et al. (2015) [30]	7045	Retrospective analysis of five administrative health databases Antipsychotics Antidepressants Benzodiazepines	All types of dementia, diagnosed between 2009 and 2011.	ICD-9	No exclusion for psychiatric comorbidity No exclusion for respite	82.71 years (6.41)	58.7%	One year follow-up	Low income, rural-living and older age (> 90 years) was associated with greater antipsychotic use. Factors associated with benzodiazepine use included female gender, lower income status, and older age (> 90 years). Factors associated with antidepressant use included three or more physical comorbidities, female gender, lower income status, younger age (< 80 years)	Low
Taipale et al. (2014) [51]	9803	Retrospective analysis of MEDALZ database 2005 Antipsychotics	Alzheimer's dementia, utilizing an antipsychotic during 2006–2009.	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 90 days	No mean or SD reported. 55% were > 80 years	68%	Three year follow-up	Among antipsychotic users, prevalence of polypharmacy (concomitant use of two or more antipsychotic medications) was 8%. 14% of these persons, had a history of psychiatric disorder of which 6% were diagnosed with schizophrenia. Factors associated with antipsychotic polypharmacy included younger age, male gender, and psychiatric illness.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Taipale et al. (2015) [31]	24,966	Retrospective analysis of MEDALZ cohort 2005 Benzodiazepines	Alzheimer's dementia	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 90 days	79 years (7)	68%	Four year follow-up	11,312 (45%) used benzodiazepines during the follow-up, of whom 30% used them for > 180 days (long-term users) Median duration of long-term use was 596 days. Factors associated with long-term benzodiazepine use were female gender, older age (> 75 years), psychiatric illness, coronary artery disease, and asthma/COPD. Prevalence of psychiatric disorder was 10% and epilepsy was 6%.	Low
Taipale et al. (2014) [51]	8920	Retrospective analysis of the "MEDALZ" database Antipsychotics	Alzheimer's dementia, utilizing antipsychotic medications	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 90 days	No mean or SD reported. 51% were > 80 years	68%	Four year follow-up	336 (4%) were classified as high dose users (defined as highest recommended doses of older adults within paper). Factors associated with high dose were history of psychiatric disorder, younger age (< 80 years), and male sex—these associations persisted even when psychiatric disorder was excluded Lower scores on the Charleston Comorbidity Index were also associated with high-dose use.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Taipale et al. (2016) [47]	67,215	Retrospective analysis of the MEDALZ 2005-2011 cohort Antipsychotics Antidepressants Anxiolytics/hypnotics Opioids	Alzheimer's dementia	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity No exclusion for respite	In the 90 year+ cohort 92.3 years (1.9) < 90 year cohort: 79.2 years (6.6)	In the 90 year+ cohort: 78.2% < 90 year cohort: 64.4%	Cross-sectional analysis 6 months following diagnosis of dementia	55.6% of those aged > 90 year used psychotropic medication compared with 48.4% of those aged < 90 years. Age > 90 years was associated with greater use of antipsychotics, benzodiazepines, memantine, and analgesic medications (paracetamol and opioids).	Low
Taipale et al. (2014) [49]	69,080	Retrospective analysis of the MEDALZ database Antipsychotics Antidepressants Benzodiazepines	Alzheimer's dementia	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 240 days	80yr (7.1)	65%	One year follow-up from time of diagnosis of dementia	Associations with antidepressants use were female gender and younger age (< 65 years). Associations with Benzodiazepine use were female gender and older age (> 85 years). Nonspecialized physicians accounted for 48–60% of first prescriptions.	Moderate
Tarvainen et al. (2021) [60]	15,384	Nested case control study utilizing "MEDALZ" database Antidepressants	Alzheimer's dementia	NINCDS-ADRA or DSM IV	Excluded schizophrenia and bipolar disorder No respite	81.5 years SD not reported	70.8%	Nested case control study of antidepressant initiators after diagnosis of dementia, following washout for 1 year prior to diagnosis.	Antidepressant initiators were more than four times more likely to have been hospitalised in the previous 2 weeks compared with those not utilising antidepressants. No difference between groups in history of hospital treated depression. Antidepressant initiators also utilized all classes of psychotropic medications more frequently.	Low

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Teipel et al. (2015) [59]	176	Retrospective analysis of participants enrolled in the DELPHI study Antipsychotics Antidepressants Antiepileptics Antidepressants	Any type of dementia	DemTec < 9	No exclusion of psychiatric comorbidity No respite	79.8 years	59.1%	Data was collected by face-to-face interview across three home visit assessments	Antipsychotic use was significantly correlated with higher NPI scores. The domains most strongly associated with use of antipsychotics included anxiety, apathy, disinhibition, and aberrant motor behavior. Antipsychotic use was not associated with domains of hallucinations or delusions. There was no association between NPI and use of antidepressant or antiepileptic medications.	Moderate
Tormalehto et al. (2017) [58]	236	Prospective 3 year study Antipsychotics Antidepressants Benzodiazepine	Alzheimer's disease, living at home with carer.	NINCDS-ADRA or DSM-IV	No exclusion for psychiatric comorbidity Respite < 90 days	76 years (6.5)	51%	Annual interviews over 3 years.	Antipsychotic use was associated with lower cognitive score and decline in activity of daily living function. Benzodiazepine use was associated with increasing neuropsychiatric inventory scores. There was no association of any psychotropic use to MMSE or CERAD-NB scores. Psychotropic use gradually increased over the three years for all classes of psychotropic medications studied.	Moderate

Table 1 (continued)

Author, year, country,	*n*	Design/psychotropic class	Dementia type	Dementia diagnostic criteria	Psych comorbidity/respite	Mean age (SD)	Females %	Analysis	Relevant findings	Risk of bias
Xiong et al. (2015) [42]	8919	Retrospective review of prescription medication records Antipsychotics	Diagnosis of any type of dementia, NACC participant	Not reported	No exclusion for psychiatric comorbidity No respite	No Mean or SD for overall cohort. 48.4% of the cohort was > 75 years	51.6%	Use of antipsychotic drugs at index visit starting in 2008.	Antipsychotic use was associated with younger age (< 70years), male gender, increased severity on Neuropsychiatric Symptom score, and greater cognitive impairment as measured by Clinical Dementia Rating Sum of boxes score. Hispanic participants utilized antipsychotics more frequently than other racial groups within this study	Moderate

Respite Temporary accommodation in full-time care; *DSM-IV* Diagnostic and Statistical Manual 4th Edition, *NINCDS-ADRA* National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's criteria, *ICD-9* International Classification of Diseases 9th Edition, *CPCSSN* Canadian Primary Care Sentinel Surveillance Network, *Demtect* Dementia Detection Screening Tool, *NIND-AIREN* National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria for VaD, *MMSE* Mini-Mental State Examination, *FTD* Fronto-Temporal Dementia, *MEDALZ* Medication use and Alzheimer's Disease Study, *SD* Standard Deviation, *CERAD-NB* Consortium to Establish a Registry for Alzheimer's Disease–neuropsychological battery, *CDR* =Clinical Dementia Rating, *Nor-PD* Norwegian Prescription Database, *achei's* Anticholinesterase inhibitors

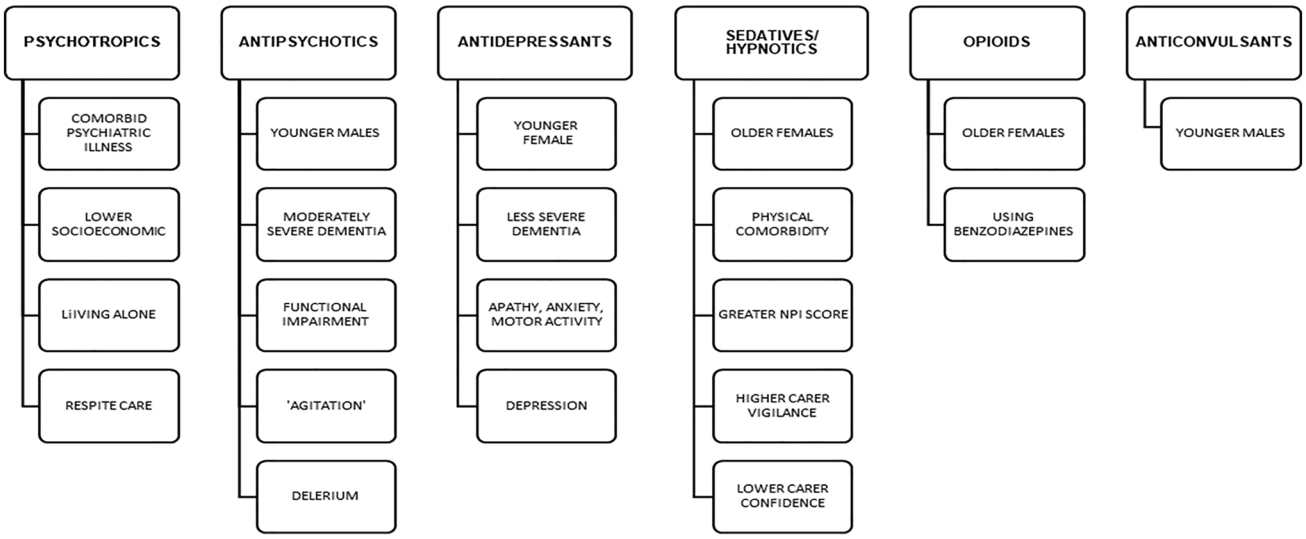

Fig. 2 Summary of identified themes

and the different classes of psychotropic medications in Fig. 2. When combined, these general and class-specific factors were grouped into higher-order themes: (1) patient related, (2) illness related, (3) environmental, (4) carer related, and (5) prescriber related or prescribing trends. Thematic analysis did not identify differences in outcome themes when studies were grouped according to type (retrospective/prospective longitudinal cohort or cross-sectional).

4.2.1 Theme 1: Patient-Related Factors

4.2.1.1 Sex Women were more commonly prescribed antidepressants, anxiolytics/hypnotics, and opioids than men, who received more antipsychotic and anticonvulsant medications. Six of the seven papers reporting on anxiolytic/hypnotic medications and sex found a significantly greater percentage of females prescribed anxiolytics/hypnotics than males [8, 27–31]. The majority of these papers (5/6) were retrospective longitudinal cohort studies of good quality and low risk of bias. One paper [25], a prospective longitudinal cohort study of good quality and low risk of bias, found no sex difference in their population of young onset people with dementia. Of the four papers that reported the use of opioids, all identified a significant difference in favor of females [8, 27, 28, 32]. Three out of the four studies were rated as good quality and low risk of bias. Eight of the ten papers that reported sex and antidepressant use found greater female use of antidepressants [8, 27, 30, 33–37]. Seven of these were longitudinal cohort studies (six retrospective and one prospective) and one was a cross-sectional analysis of a prospective cohort). Five of the eight studies were good quality and low risk of bias. The two remaining papers found no difference between males and females [25, 38]. Of these two papers, one represented a unique younger onset dementia population [25], while the other investigated carer and care recipient factors rather than sex, which may have influenced the outcomes of this finding [38]. Both were of good quality and low risk of bias. One was a prospective longitudinal cohort, the other was a cross-sectional analysis of a retrospective cohort. Antipsychotics were utilized more frequently in males compared with females in six papers [27, 36, 39–42]. Of these two were retrospective cross-sectional analyses, two were prospective longitudinal cohorts, and two were retrospective longitudinal cohorts. Two papers, both retrospective longitudinal cohorts, reported greater use in females [8, 43] and one, a retrospective longitudinal cohort, identified that females were prescribed antipsychotics more commonly prior to diagnosis compared with males [44]. The use of anticonvulsant drugs was reported in one study, where males used anticonvulsants significantly more than females ($p < 0.001$) [45].

4.2.1.2 Ethnicity There was sparse data relating to ethnicity. One paper [46] investigated this as the primary objective, identifying that anxiolytic use was more common in African American people with dementia, while antipsychotics were used more frequently in non-Hispanic white people. No consistent trend was identified in the other available papers reporting on ethnicity as secondary outcomes [8, 38, 42].

4.2.1.3 Age There were 20 papers available for synthesizing age and psychotropic use. There was increased use of psychotropics in older individuals (> 80 years) before dementia diagnosis and increased association with psychotropic use in younger individuals (< 75 years) immediately following

diagnosis [9, 28, 44]. All three of these studies were of good quality and low risk of bias. A second trend was identified for "very old" people (defined in the paper as > 90 years) in whom the use of psychotropics appeared to be higher than those < 90 years old [47]. Younger individuals (< 75 years) received more antidepressant, antipsychotic, and anticonvulsant medications [8, 37, 42, 48], while older individuals were prescribed more benzodiazepines and opioids [27, 28, 32, 49]. There was a consistent trend for younger individuals to have more psychotropic polypharmacy [9, 50, 51]. These findings were consistent across both the longitudinal and cross-sectional studies.

4.2.1.4 Psychiatric Comorbidity The use of psychotropic polypharmacy was significantly associated with having a psychiatric history in four papers [9, 28, 50, 51]. Although there was no significant association between a history of mental disorders and antipsychotic use in Eichler et al.'s study, sample numbers were low, with only 140 participants included in the factor analysis, of whom 22 were on antipsychotic medication [52].

A history of depression and antidepressant use was associated with increased use of antipsychotics [9, 40, 41, 44, 50, 51, 53, 54]. The use of benzodiazepines and/or opioids was significantly associated with a history of prior substance abuse [28, 29, 32].

Highly significant associations with prior diagnoses of psychiatric illness (schizophrenia, bipolar disorder, or depression) were also demonstrated for long-term benzodiazepine use ($p < 0.0001$) [31] and high-dose antipsychotic use ($p < 0.0001$) [55]. Anticonvulsant use was also significantly associated with depression, schizophrenia, and bipolar disorders ($p < 0.001$ for all), although only formally investigated in one study [45].

4.2.1.5 Pain Only two studies specifically investigated pain in relation to psychotropic use. Grace et al. [38] reported a significant association between pain and antipsychotic use. Hamina et al. [56] identified that opioid initiation triggered an immediate increase in benzodiazepine and antipsychotic use, with a nonsignificant decrease in the use of these agents up to 6 months post-opioid initiation.

4.2.2 Theme 2: Illness-Related Factors

4.2.2.1 Severity of Dementia Antipsychotic use did not increase in parallel with the severity of cognitive impairment. Antipsychotic use was significantly associated with moderately severe dementia (as opposed to mild or severe) in all three papers that reported on this [48, 52, 57]. One paper found no association between cognition (measured by the Mini-Mental State Examination) and antipsychotic use; however, Mini-Mental State Examination scores were not categorized as mild, moderate, or severe, and a cumulative value was used, which may have influenced the findings [58]. Two papers reported a significant association between antipsychotic use and greater severity on the Clinical Dementia Rating sum of boxes scale [42, 58]. No trend was identified between cognitive functioning and other classes of psychotropics. All the papers above were rated as moderate risk of bias apart from one [48], which was rated a low risk of bias. Three of the studies were cross-sectional in nature [42, 48, 52] and two were longitudinal cohorts of up to 1 year follow-up [57, 58].

4.2.2.2 Functional Ability/Activities of Daily Living Independence There was a significant association between antipsychotic use and greater impairment in activities of daily living across the six studies that reported on this [38, 40, 41, 48, 52, 58].

4.2.2.3 Neuropsychiatric Symptoms Antipsychotic use was most closely associated with Neuropsychiatric Inventory (NPI) scores. Six of eight studies demonstrated a significant association between increasing NPI scores and antipsychotic use [26, 42, 48, 54, 57, 59], while two did not [25, 58]. No consistent trend was identified regarding NPI scores and antidepressant or anxiolytic/hypnotic medication use.

4.2.3 Theme 3: Environmental Factors

4.2.3.1 Socioeconomic Lower socioeconomic status was generally associated with the use of benzodiazepines, antipsychotics, and opioids [8, 28, 32, 40–42, 45, 48, 50]. Bargagli et al. [39] found that lower socioeconomic status was associated with the use of the typical antipsychotics specifically, while Grace et al. [38] found no association between psychotropic use and income adequacy overall; however, individual psychotropic class analysis was not available. There was no consistent trend in antidepressant use and socioeconomic status in two studies [33, 34].

4.2.3.2 Living Alone All four papers that investigated this association demonstrated a positive association between psychotropic use and living alone. Two of these papers reported a statistically significant association [35, 48]. Eichler et al. [52] reported a trend, but following multivariate analysis, no significant difference; however, the numbers in this study were small and may have influenced the outcome. Arbus et al. [33] reported a numerically greater percentage of those living alone using antidepressants; however, no p value was reported.

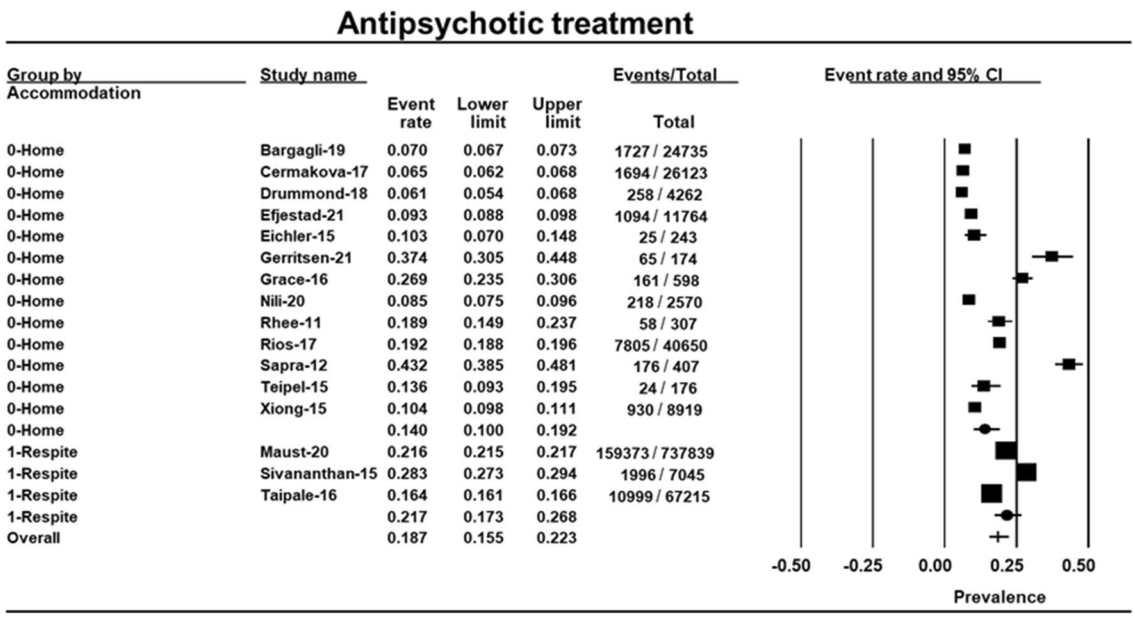

Fig. 3 Forest plot of antipsychotic treatment by respite allowance. Respite: temporary full-time care/hospitalization was allowed during the study period. Home: allowance for temporary full-time care or periods in hospitalization were excluded or not described

4.2.3.3 Hospitalization Two papers investigated the association between recent hospitalizations and either antipsychotic [60] or antidepressant initiation [53]; both reported a significant positive association.

4.2.4 Theme 4: Carer-Related Factors

Only three papers investigated carer-related factors in psychotropic use. In Grace et al.'s study [38], greater caregiver vigilance was associated with significantly greater anxiolytic/hypnotic use ($p \leq 0.05$), and greater caregiver dementia knowledge was associated with greater antidepressant use ($p = 0.02$), while greater caregiver confidence was associated with significantly less use of anxiolytics ($p = 0.04$). Rhee et al. [48] reported significantly lower rates of depression in carers of people living with dementia being treated with antipsychotics ($p < 0.001$), while people with dementia were significantly less likely to be taking an antipsychotic if the caregiver was depressed ($p = 0.005$). There was no significant association between antidepressant use and caregiver burden reported by Arbus et al. [33].

4.2.5 Theme 5: Prescriber-Related Factors

4.2.5.1 Concomitant Psychotropic Use Definitions of polypharmacy differed between studies. Orsel et al. [9] reported a prevalence of 18.3% of two or more psychotropic agents prescribed concomitantly, while Maust et al. [50] found that 13.9% were prescribed three or more central nervous system-active medications for at least 30 days. The use of three antipsychotic agents was reported in 3.9% of the sample in a study by Aigbogun et al. [57].

4.2.5.2 Time Course of Psychotropic Use The first 6 months after dementia diagnosis was identified as a risk factor for initiating psychotropic medication. Although psychotropic use was already evident years before dementia diagnoses, the incidence of use tended to peak between diagnosis and 6 months, especially for antipsychotics and antidepressants [37, 44]. Once initiated, psychotropic use appeared to continue beyond 6 months into years, with long-term psychotropic exposure occurring for all psychotropic medication classes [9, 25, 30–32, 37, 45, 56, 58, 61]. This was consistent across study types.

4.3 Meta-analysis

The range of meta-analyses able to be performed was limited to available published appropriate data and that obtained on request. The following analyses were conducted in eligible included studies: antipsychotic use and psychiatric comorbidity; antipsychotic use and respite allowance; antipsychotic use and sex; antidepressant use and psychiatric comorbidity; antidepressant use and respite allowance; anxiolytic/hypnotic use and respite allowance; and study country and antipsychotic, antidepressant, and opioid use.

There were insufficient data to conduct meta-analyses for opioid or anticonvulsant use. Two authors provided raw data; however, this was insufficient for a meta-analysis of age or gender associations [15, 25].

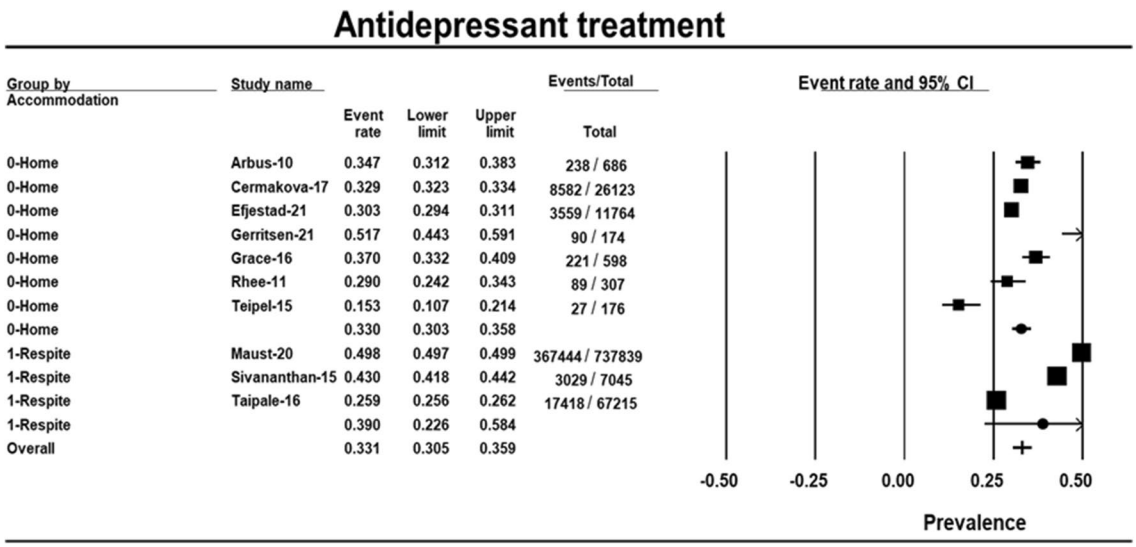

Fig. 4 Forest plot of antidepressant treatment by respite allowance. Respite: temporary full-time care/hospitalization was allowed during the study period. Home: allowance for temporary full-time care or periods in hospitalization were excluded or not described

4.3.1 Antipsychotic Treatment

Figure 3 shows the event rates and 95% confidence intervals (CIs) for the prevalence of any antipsychotic treatment in people living with dementia grouped by allowances for respite (i.e., whether the study overtly limited or excluded any time in either temporary facility-based care or hospitalization). There was a high degree of within-group heterogeneity, defined as an I^2 value above 50%. ($Q = 9308$; $df(Q) = 16$; $p < 0.001$; $I^2 = 99.8$; see Table S1). There was evidence of publication bias, as indicated by Egger's test ($t = 2.48$; $df = 15$; $p < 0.05$). Trim and fill analysis did not identify any of the included studies that might have been biased toward higher rates of antipsychotic use.

There was a significant association between the prevalence of antipsychotic medication and allowances for respite (temporary facility-based care/hospitalization) (see Fig. 3 and Table S1). Kester et al.'s study [40] was excluded from this analysis because this variable was not stated. Antipsychotic use was lower in studies excluding any temporary respite or hospitalization (OR 0.140; 95% CI 0.100, 0.192; $N = 13$) compared with those with respite allowances [OR 0.217, 95% CI 0.173, 0.268; $N = 3$; $q = 4.85$; $df(Q) = 1$; $p = 0.028$].

Subgroup analysis indicated significant differences in antipsychotic use and the presence or absence of a psychiatric diagnosis (see Table S1). Antipsychotic rates were significantly lower in those without a comorbid psychiatric diagnosis (OR 0.082; 95% CI 0.058, 0.114; $N = 4$) compared with those with a comorbid psychiatric diagnosis (OR 0.180; 95% CI 0.124, 0.253; $N = 6$) or studies that did not report this variable [OR 0.182; 95% CI 0.136, 0.238; $N = 7$; $q = 15.02$; $df(Q) = 2$; $p < 0.001$]. There were no significant differences in antipsychotic rates and the country where studies were conducted (USA versus non-USA; see Table S1) or antipsychotic rates and gender (OR 1.034; 95% CI .931, 1.124; $p = 0.433$; $N = 10$ studies).

4.3.2 Antidepressant Treatment

Figure 4 shows the event rates and 95% CIs for the prevalence of any antidepressant medication in people living with dementia grouped by respite allowance as above. There was a high degree of within-group heterogeneity [$Q = 16960$; $df(Q) = 9$; $p < 0.001$; $I^2 = 99.9$; see Table S2]. There was no evidence of publication bias, as indicated by Egger's test ($t = 1.68$; $df = 8$; $p = 0.13$). Trim and fill analysis did not identify any of the included studies that might have been biased toward higher rates of antidepressant use.

There was no significant difference between the prevalence of antidepressant treatment and respite allowances (see Fig. 4 and Table S2). Those studies that precluded respite allowances had similar rates of antidepressant drug use (OR 0.330; 95% CI 0.303, 0.358; $N = 7$) as those allowing temporary respite care [OR 0.390; 95% CI 0.226, 0.584; $N = 3$; $q = 0.42$; $df(q) = 1$; $p = 0.519$]. Subgroup analyses indicated no significant differences in antidepressant drug use and the presence or absence of a comorbid psychiatric diagnosis ($p = 0.976$) or country where the study was conducted ($p = 0.408$; see Table S2).

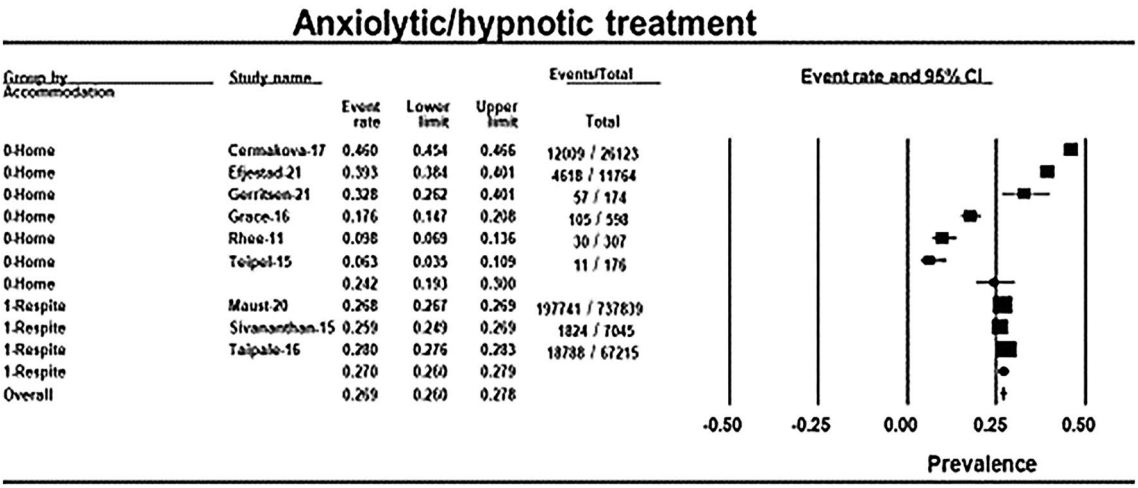

Fig. 5 Forest plot of anxiolytic/hypnotic treatment by respite allowance. Respite: temporary full-time care/hospitalization was allowed during the study period. Home: allowance for temporary full-time care or periods in hospitalization were excluded or not described

4.3.3 Anxiolytic/Hypnotic Treatment

Figure 5 shows the event rates and 95% CIs for the prevalence of any sedative/hypnotic medication in people living with dementia grouped by respite allowance. There was a high degree of within-group heterogeneity [$Q = 5316$; $df(Q) = 8$; $p < 0.001$; $I^2 = 99.9$; see Table S3]. There was no evidence of publication bias, as indicated by Egger's test ($t = 0.87$; $df = 7$; $p = 0.414$). Trim and fill analysis did not identify any of the included studies that might have been biased toward higher rates of anxiolytic/hypnotic use. There were no significant differences between the prevalence of anxiolytic/hypnotic use and respite allowances or the country where the study was conducted (see Fig. 5 and Table S3).

5 Discussion

This study is, to our knowledge, unique because it is the first systematic review and meta-analysis of factors associated with psychotropic use in people with dementia living in the community. Although there was heterogeneity identified, thematic analysis did not identify differences in outcome when studies were grouped according to type. In the majority of studies, the risk of bias was low or moderate. Five broad categories of factors emerged from the thematic analysis: (1) patient-related (age, sex, comorbidities), (2) illness-related (severity, functional impairment), (3) environmental (living alone, periods of full-time care), (4) carer-related, and (5) prescriber-related trends. Meta-analysis key findings included significant associations between psychotropic use and psychiatric comorbidity and allowances for respite, specifically for antipsychotics.

Regarding patient factors, age and sex emerged as key factors in the thematic synthesis. Findings concerning age have important implications for symptom interpretations. From the thematic synthesis, ages < 75 years and > 90 years were associated with increased use of psychotropics in general. This was more clearly reflected in class-specific analyses, with antidepressants, antipsychotics, and anticonvulsants being used in younger individuals and benzodiazepines and opioids in older individuals. It is difficult to interpret these findings given the lack of information about reasons for prescribing and the variability of age group definitions. However, there may be a demographic bias concerning risk assessments and behavioral expressions that influence the selection of medications, warranting empirical examination. Moreover, given the normalization or expectation of depression associated with aging [62], it is not surprising that older patients are less likely to be prescribed antidepressants.

Although thematic synthesis identified a trend toward males receiving antipsychotics more than females, this was not demonstrated in the meta-analysis of ten studies with adequate data. Several reasons could account for this, including the limited data amenable to meta-analysis; limited information about the timing, type, or dose of antipsychotic being used; and reasons for use, all of which have sex-specific implications.

The need for psychotropic medication is very much in the eye of the beholder (or perhaps the prescriber), often driven by the degree to which behavior or symptoms are considered problems (i.e., obvious or disruptive) or, conversely, significant and worthy of treatment; a finding consistent with that observed in long-term care [63]. The most common reasons for prescribing antipsychotic medications were

Table 2 Practical strategies for optimizing prescribing decisions

1. *What am I treating?* Is medication appropriate for the symptom or problem? Is the symptom a manifestation of something else?
2. *Who am I treating?* Am I treating a patient living with dementia or their carer? Am I treating a modifiable environmental trigger that is better managed without pharmacotherapy? Have I considered my motivations and reasons that may be influencing my decision to prescribe psychotropic medications in each situation?
3. *How will I measure the response to this treatment?* Is the medication beneficial? What are the target outcomes, and how will I measure this? Are there side effects, and when will I stop the medication?
4. *Have new medications been reviewed?* How can I ensure psychotropics initiated in a hospital or temporary care elsewhere are for short-term emergency use only? Am I regularly monitoring this?
5. *Expertise and collaboration.* Am I using multidisciplinary team skills and expertise to facilitate a comprehensive approach to support the patient and their carer/family?
6. *Supports.* How can I increase support and training for caregivers to use nonpharmacological strategies for behavioral symptoms and changes that occur over time?

excessive motor activity, anxiety, agitation, and even apathy, rather than delusions, hallucinations, or severe aggression. The reasons for these associations remain speculative but could reflect a symptom description/classification issue [14], failure to identify or misidentification of the causes of behaviors (i.e., unmet need, pain, delirium, or illness) [64], or lack of skills and resources available to manage these behaviors [65].

The most robust illness-related finding regarding psychotropic use in this population was a decline in functional ability. The direction of causality is unclear here—that is, whether psychotropic medications cause functional decline or functional decline precipitates use. A hypothetical mechanism for this is a possible relationship between functional decline and care demands, unmet needs of the recipient, and the consequent effects on carer stress [66]. Elucidating what it is about functional decline, independent of cognitive decline or neuropsychiatric symptoms, remains to be investigated and would provide a critical piece of information needed to optimize interventions and support.

Regarding environmental factors and patterns of prescribing, an apparent prescribing trajectory emerged from the literature, with psychotropic prescribing often starting years before dementia diagnoses. Once people are on this trajectory, they appear to continue receiving psychotropic medications, often for prolonged periods. This suggests that the culture of prescribing is initiated before or around the diagnosis period and then continued and increased during certain times throughout the illness. This correlates with other studies suggesting that a dementia diagnosis is associated with the prescribing of psychotropic medications [7, 67].

Points of contact with healthcare providers and different care settings were identified as another environmental factor associated with increased psychotropic use emerging in both the thematic synthesis and meta-analysis. Such points of contact included periods of hospitalization and respite in temporary care. Possible explanations are that temporary time in residential care or hospitalization could relate to acute illness and delirium [68], increased changed behaviors [69], and/or care needs or carer burnout [70]. Again, this is hypothetical and needs empirical testing, but identifying this might help raise awareness among clinicians to avoid the pitfalls of starting new psychotropic medications that are then continued over time, an ideal opportunity for intervention, improved multidisciplinary collaboration, and medication review practices [71, 72].

Living alone was also associated with psychotropic use, potentially pointing to unmet needs being treated pharmacologically. These needs could relate to difficulties navigating services and accessing community supports [73] and increased rates of hospitalization and placement [74].

This review identified the dearth of information regarding carer and caring dyad influences on psychotropic use in this setting. What little literature was available suggested that carer symptomatology [38] and medication use [75] can influence prescribing in the care recipient. Therefore, this relationship deserves greater attention, begging the question: whom are we treating, and are there alternative approaches to lowering the carer burden and supporting carers rather than medicating the person living with dementia?

Despite the availability of guidelines to manage behavioral symptoms in the context of dementia, the implementation and applicability of these to clinical practice remain suboptimal [76]. By addressing identified gaps in understanding the factors driving psychotropic medication use, we will be better able to design and implement interventions to support the needs of this population and their families/carers.

Notwithstanding the gaps in the results relating to the prescriber, some practical questions emerged from this review that might raise awareness and inform prescribers when assessing psychotropic use and prescribing for their patients with dementia in this setting as described in Table 2.

While the focus of quality prescribing has hitherto targeted residential care settings, there is an equal imperative to promote quality prescribing initiatives for those living in the community. This review has shone a light on home-based

care as a target for quality prescribing interventions and as an available opportunity for people living with dementia.

This study's limitations relate mostly to the type of data available, limiting meta-analysis. Further, crude rates of antipsychotic prescribing do not provide any information on the potential appropriateness of use; hence, all possible prevalence studies were not included in this systematic review. This paper was not designed to determine causality, but rather to examine potential factors that were associated with use of psychotropics to provide a greater understanding as to how and why these medications are used for more targeted future research and targeted quality interventions. Five of the 39 studies were cross-sectional, rendering limitations not only in causality but in temporality. The nature of the illness is complex, and while assumptions can be made, there may be multiple confounders influencing the use of psychotropics at an individual level for which data is unavailable. Gray literature was not included due to the potential risk of quality and publication bias. This study had a strong Western bias because no studies were from Asia or Africa.

6 Conclusions

In this systematic review and meta-analysis, we have identified a range of factors associated with the use of psychotropic medication in people living with dementia in the community The reviewed studies suggest that while psychotropic prescribing is prevalent in this population group, a clear understanding as to the reasons why these medications are being used is not available from existing literature. While associated factors can be identified for specific psychotropic classes, there is a clear need to develop targeted research and programs to truly understand what is driving this medication use. While some psychotropic medication use may very well be appropriate and needed in some circumstances (e.g., for treatment of major depression or psychotic symptoms), it would seem that, from the analysis, there is use occurring in circumstances and for reasons that are ill defined or potentially inappropriate. This study has highlighted the very clear need for further targeted research to be conducted. The identified factors provide a much-needed context for this research and future quality improvement programs to be implemented in a targeted way.

Qualitative studies that capture the voice of the person living with dementia at home and their carers, as well as examining aspects of their relationship, are urgently needed to better understand these findings.

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Declarations

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