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REVIEW ARTICLE

Are the Safety Profiles of Antipsychotic Drugs Used in Dementia the Same? An Updated Review of Observational Studies

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Abstract With an increase in the global prevalence of dementia, there is also an increase in behavioural and psychological symptoms of dementia (BPSD) for which antipsychotic drugs are often used. Despite several safety warnings on antipsychotic use in dementia, there is little evidence to support the efficacy of antipsychotics in individual BPSD symptoms or to evaluate the drug safety profile by individual antipsychotic drug. There is emerging but scarce evidence that suggests an inter-drug variability between antipsychotic safety outcomes in BPSD. The objective of this review was to examine the existing literature on antipsychotic drug use in dementia patients; in particular to see whether inter-drug differences regarding antipsychotic safety were reported. A literature search was conducted for observational studies published in the English language from 2004 to 2014 that reported the risk of all-cause mortality, cerebrovascular events, pneumonia and other outcomes such as hip/femur fracture, deep vein thrombosis (DVT) and hyperglycaemia. Six of 16 mortality studies (38 %), 7 of 28 stroke studies (25 %), 1 of 6 pneumonia (17 %) studies and 2 of 6 fracture studies (33 %) investigated inter-drug safety outcomes in elderly patients/dementia patients, while to our knowledge, there are no studies investigating the inter-drug variation of deep-vein thrombosis and hyperglycaemia risk. The results of the observational studies provide mixed results on the safety of antipsychotics in BPSD but it is clear that there are differences between the safety profiles of antipsychotic drugs. Robust evidence of such inter-drug variability could significantly improve patient safety as antipsychotics become more targeted to clinical risk factors.

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Key Points

Despite increasing awareness of the safety issues surrounding antipsychotic drug use in behavioural and psychological symptoms of dementia (BPSD), there is currently very limited information on the inter-drug variation in risk as the vast majority of studies focus on all antipsychotics as a group or on atypical/conventional antipsychotics as a class.

It is becoming apparent that there is indeed a difference between the risks associated with individual antipsychotic drugs in BPSD. Robust evidence of the risks associated with individual antipsychotic drugs could significantly improve the standards of clinical care by tailoring the specific therapeutic/safety drug profiles to the clinical needs of individual patients.

1 Introduction

Globally, the estimated number of patients with dementia was 25 million in 2000 and is projected to rise to 63 million by 2030 [1]. The clinical manifestations of dementia consist of cognitive and/or memory deterioration with progressive impairment of activities of daily living, as well as a variety of behavioural and psychological symptoms (BPSD) [2, 3]. These neuropsychiatric symptoms occur in more than 90 % of patients with dementia and present a significant challenge for clinicians as well as caregivers [3]. BPSD is not a single behaviour but comprises several symptoms, such as agitation, psychosis and mood

disorders, which usually co-occur and often recur. Patients with BPSD are more likely to need physical restraint, have a higher risk of early institutionalization and a higher risk of mortality [4–6]. In addition, BPSD negatively affects the quality of life of caregivers and other residents, if in a nursing home [7, 8]. The aetiology of these symptoms is still not fully known.

Antipsychotics are often the first-line treatment for BPSD. They are generally distinguished as conventional (first-generation) or atypical (second-generation) antipsychotics. Conventional agents include butyrophenones (e.g. haloperidol), phenothiazines (e.g. chlorpromazine and thioridazine) and several others (e.g. indoles, thioxanthenes). Conventional antipsychotics were approved in the 1950s mainly for the treatment of schizophrenia. Since then, these agents have also been used for the treatment of a broad spectrum of psychiatric disorders, including BPSD, despite a lack of scientific evidence supporting their use in dementia [9]. Currently, atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine and amisulpride. The receptor-binding profile among atypical antipsychotics differs substantially across different compounds, such that these drugs cannot be truly considered a unique homogeneous therapeutic class [9–13]. Atypical antipsychotics were initially licensed in the 1990s and approved by the US FDA exclusively for the treatment of schizophrenia. Nowadays, they are also approved for the treatment of bipolar mania, while their use in dementia has remained off-label. Only risperidone has been approved for the treatment of aggression in patients with Alzheimer's disease in most European countries. Despite their off-label status in dementia, atypical antipsychotics have become the new standard of care for BPSD owing to their reported advantages over conventional agents, particularly a lower incidence of extrapyramidal symptoms (EPS) and tardive dyskinesia [9]. In the late 1990s, atypical agents accounted for more than 80 % of antipsychotic prescriptions in dementia in US nursing homes as well as in Canada [14]. In Europe, the use of atypical antipsychotics was lower even though it increased dramatically early after their introduction on the market [15].

1.1 Efficacy of Antipsychotics in Dementia

To date, more than 20 placebo-controlled, randomized clinical trials (RCTs) have investigated the efficacy of atypical antipsychotics for the treatment of BPSD, of which some were not published in full [16]. In their systematic review of 16 RCTs on atypical antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole) for treatment of aggression, agitation and psychosis in dementia, Ballard and Waite concluded that risperidone and olanzapine have a modest efficacy in reducing aggression and psychosis, but both drugs were associated with serious adverse cerebrovascular events (CVEs) and EPS [16]. Another meta-analysis of seven RCTs of atypical antipsychotics (risperidone, olanzapine and quetiapine) reported neither a statistically nor a clinically significant difference in effectiveness as compared with placebo [17]. The findings from the meta-analyses were confirmed by a recent report of the CATIE-AD study which concluded that adverse effects (olanzapine, risperidone, quetiapine vs. placebo) offset the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease [18]. More recently, a systematic review on the efficacy of atypical antipsychotics for off-label use in the treatment of elderly dementia patients with BPSD identified 14 placebo-controlled trials and assessed the efficacy of atypical antipsychotics using a total global outcome score, including symptoms such as psychosis, mood alterations, and aggression. This systematic review reported small but statistically significant effect sizes ranging from 0.12 and 0.20 for aripiprazole, olanzapine, and risperidone, but indicated an absence of benefit with quetiapine [19].

In general, these RCTs had a short duration which may not reflect the use of antipsychotic drugs in clinical scenarios. In addition, a placebo-controlled trial of 4 or more weeks' duration may present significant potential for patient selection bias. This is because subjects with more severe psychosis or agitation may not choose to be enrolled into a placebo-controlled trial as their symptoms are too severe to take the chance of getting a placebo treatment. This leaves more mildly psychotic or agitated subjects being enrolled into placebo-controlled trials, resulting in an underestimation of the positive efficacy of these agents for psychosis and agitation. BPSD RCTs also present limitations when they include patients living at home, in senior independent or non-locked assisted-living environments, rather than patients living in locked assisted-living or nursing home facilities. The latter are where the majority of antipsychotics are most commonly used and are where the most severe behaviours are encountered. A further limitation encountered in RCTs may be a lack of equivalence between the antipsychotic doses used, potentially favouring some drugs over others.

To our knowledge, at present no published data from double-blind RCTs on patients with dementia are available for amisulpride, clozapine, paliperidone, asenapine, and ziprasidone, which are seldom or never used in BPSD [9]. Overall, there is also very limited evidence of any benefit of antipsychotics in the treatment of BPSD over periods longer than 12 weeks, despite the fact that up to 60 % of older people with dementia receive treatment with antipsychotics for more than 6 months [20].

1.2 Safety of Antipsychotics in Dementia

The safety profile of atypical and conventional antipsychotics has been questioned in recent years, as demonstrated by a number of warnings that have been issued by regulatory agencies [21]. Despite all safety warnings, recent studies document a persistent wide use of antipsychotics in dementia due to the lack of alternative pharmacological options. Valiyeva et al. [22] demonstrated that the warnings slowed growth in the use of atypical antipsychotics among patients with dementia, but they did not reduce the overall prescription rate of these drugs in Canada. Similarly, other studies in the US and Europe observed a reduction in the use of atypical antipsychotics in dementia as a result of the initial safety alerts [23–25]. This decreasing trend was, however, counterbalanced by a switch towards conventional antipsychotics, even though these are reported to have a similar increase in mortality risk [23, 24]. For all these reasons, a re-evaluation of the possible risk minimization effects of the safety warnings, as well as a thorough assessment of the long-term mortality of each single antipsychotic in dementia, is much needed.

Various safety concerns have been encountered with antipsychotic use, including all-cause mortality, cardiac arrhythmias, peripheral vascular effects, metabolic effects, pneumonia and cerebrovascular accidents. Very little attention has, however, been given to the safety issues related to antipsychotic withdrawal in BPSD, an area that warrants further investigation, particularly because the use of antipsychotics in BPSD is generally recommended in the short-term [26, 27].

The importance of studies targeting antipsychotic use in dementia patients is highlighted by age-related pharmacokinetic changes as well as potential drug–drug interactions that can result in higher and more variable drug concentrations in this population, thus further increasing the risk of toxicity [8, 28]. In addition, age-related pharmacodynamic changes generally require antipsychotic dose adjustment in elderly persons [29]. This is because the clinical effect of a drug is a function of the affinity with the target, the drug concentration at the site of action (depending on the absorption, distribution, metabolism, excretion [ADME]) and patient characteristics such as age and sex [30]. Nevertheless, there are few such pharmacokinetic studies that assess the ADME parameters in dementia patients [28]. Drug metabolism and excretion may vary substantially in older persons and current clinical recommendations suggest prescribing only a quarter to half of the defined daily dose of antipsychotics in geriatric patients [30] in the absence of more detailed pharmacokinetic evidence.

In light of the wide use of antipsychotics in dementia patients, as well as the uncertainty about their actual safety profile in clinical practice, we conducted an updated review of currently known safety issues of individual antipsychotics.

2 Methods

Pubmed was searched for the following terms: 'antipsychotics', 'antipsychotic drugs', 'antipsychotic agents' and 'mortality', 'all-cause mortality', 'death' or 'CVEs', 'cerebrovascular event', 'CVE', 'stroke', 'ischaemic stroke', 'ischemic stroke', 'haemorrhagic stroke', 'hemorrhagic stroke', 'transient ischaemic attack', 'transient ischemic attack', 'TIA' or 'pneumonia', 'community-acquired pneumonia', 'acute chest infections', 'bronchopneumonia' or 'hip fracture', 'femur fracture', or 'deep vein thrombosis', 'DVT', or 'hyperglycaemia', 'hyperglycemia'. Studies were included if they were observational, cohort, case–control or self-controlled studies published in the English language from 2004 to 2014. Studies were included irrespectively of whether the reference group was unexposed patients or not and with no restrictions related to diagnostic categories.

References of relevant original research as well as review articles were hand-searched to identify further studies. Two investigators (GT and JS) independently examined the titles and abstracts and obtained full texts of potentially relevant papers. Any disagreement was resolved through consensus. Information on study design, setting/data source, study population, outcomes measured, exposure and main findings (risk estimates where possible) were extracted for each study and tabulated. All confidence intervals reported were at the 95 % level.

3 Results

3.1 All-Cause Mortality

In April 2005, the FDA issued a warning to inform health professionals that the mortality rate among elderly patients with dementia-related behavioural disorders receiving an atypical antipsychotic was higher than that observed in placebo-treated patients [31]. One of the initial alarm triggers of antipsychotic safety was a pooled analysis of RCTs by the European Medicines Agency (EMA) in 2004, which reported a twofold increased risk of all-cause mortality with olanzapine compared with placebo [32]. A more extensive analysis was carried out by the FDA shortly after, in 2005. The FDA meta-analysis included 17 RCTs that investigated all-cause mortality in olanzapine, risperidone, quetiapine and aripiprazole, and reported a risk that was also approximately twofold [31]. Further similar analyses that arrived at similar conclusions were carried out in 2005. A meta-analysis of five olanzapine, five risperidone, three

aripiprazole and three quetiapine trials that included only elderly dementia patients found that, overall, all these drugs carried a risk of excess mortality [33]. In June 2008, the FDA stated that the conventional antipsychotics share a similar risk of increased mortality with the atypical antipsychotics [34].

Several subsequent observational studies investigated the risk of antipsychotic-related all-cause mortality in larger populations than RCTs and over longer exposure periods, and comparing the risk of atypical versus conventional antipsychotics or non-use (Table 1). One such study was a cohort study published in the US shortly after the FDA warning and which included 22,890 elderly atypical and conventional antipsychotic users (almost 50 % with dementia) [35]. This study found a significant 30 % increased risk of mortality with conventional antipsychotics compared with atypical antipsychotics. Similar results were found by a cohort study in British Colombia, namely a 26 % increased risk of mortality within 180 days with conventional versus atypical antipsychotics in elderly patients, of whom, however, a lower proportion had dementia [36]. Another cohort study found that there was a 17 % lower risk of mortality with atypical antipsychotics compared with conventional antipsychotics in dementia after 12 months [37]. None of these studies evaluated the risk of all-cause mortality associated with individual antipsychotics. The increasing evidence led the FDA to issue another warning in June 2008 on the high risk of mortality with conventional atypical antipsychotic use [38].

The risk of mortality was found to increase with increasing dose and was highest shortly after exposure [35, 36, 39, 40]. While the expanding research base has highlighted several relevant safety issues, several others, such as the differential risk of mortality associated with individual antipsychotics, remain unknown. A recent observational study by Huybrechts et al. [41] suggested that the risk of mortality is differential, being highest for high-dose haloperidol [high dose vs. low dose hazard ratio (HR) 1.84 (1.38–2.43), with high and low dose defined using the median daily dose of chlorpromazine equivalent dose as a cutoff point) and lowest for low-dose quetiapine [medium dose vs. low dose HR 1.02 (0.89–1.18), with medium- and low-dose quetiapine defined as 50–75 and 0–50 mg of chlorpromazine equivalent doses, respectively]. However, Huybrechts et al. [42] investigated outcomes of only five antipsychotics (haloperidol, aripiprazole, olanzapine, quetiapine and ziprasidone, with risperidone as comparator), omitting several others. Two other recently published observational studies support the finding that mortality risk varies by individual antipsychotic. One study reported that the highest mortality rates were for haloperidol [relative risk (RR) 1.54 (1.38–1.73)], while the lowest were for quetiapine [RR 0.73 (0.67–0.80)] [42]. The other study, which included only vascular dementia patients, reported higher but not statistically significant mortality rates for quetiapine [HR 1.13 (0.92–1.37)] and lower mortality rates for risperidone [HR 0.87 (0.60–1.27)] [43].

The investigation of antipsychotic-related risk has also been carried out in more vulnerable subpopulations of dementia patients, such as those living in nursing homes [41, 44–48]. This is of particular importance as elderly persons living in nursing homes are likely to be more frail than their community-dwelling counterparts [49]. The comparative risk of specific-cause mortality for individual antipsychotic agents is also poorly characterized, while more general comparisons between conventional and atypical antipsychotic classes have been investigated [50]. A recent study found a differential risk of specific causes of mortality in nursing homes, but included only one conventional antipsychotic compared with five atypical agents [41]. Huybrechts et al. found that haloperidol users in nursing homes had a higher risk of mortality compared with risperidone [HR 2.07 (1.89–2.26)], and quetiapine users had a lower mortality risk [RR 0.81 (0.75–0.88)]. It should be noted that the findings of some studies did not support this higher risk associated with conventional antipsychotics, or even any antipsychotics in dementia, but such studies tended to have very small populations and for this reason should be interpreted in the context of their limitations [51, 52]. Several specific causes have been suggested to be at the root of antipsychotic mortality, including CVEs, pneumonia, peripheral vascular effects and metabolic effects, all of which are explored in further detail below.

A general consideration in these mortality studies, as well as other observational studies described below, relates to the comparison group used. As can be seen from Tables 1, 2, 3 and 4, the comparison group often consists of non-users of antipsychotics. This may result in the exposed and unexposed groups having important differences in dementia severity and overall frailty that increase the risk of death for exosposed groups independently of antipsychotic use alone.

3.2 Cerebrovascular Effects

In October 2002, the marketing authorization holder of risperidone notified all Canadian healthcare professionals that risperidone users had a higher rate of CVEs than placebo [53]. In March 2004, the UK Committee on Safety of Medicines recommended that health professionals avoid off-label use of atypical antipsychotics in elderly individuals with BPSD, particularly in those with a high baseline risk of stroke [54], due to the observed CVE risk associated with these antipsychotics. At that time, information was reported only for olanzapine and risperidone although a

Table 1 Observational studies investigating the risk of mortality associated with antipsychotic use in elderly dementia patients

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Suh and Shah [52]	Prospective cohort study	Semi-hospitalized, long-term-care nursing home in Seoul	Dementia patients ($N = 273$)	All-cause mortality	All APs (non-use as comparator):	Adj. RR: 1.28 (1.13–1.44)
Wang et al. [35]	Retrospective cohort study	Pennsylvania, Medicare	Patients ≥65 years ($N = 22,890$)	All-cause mortality	CAPs vs. AAPs	Adj. RR: Within 180 days: 1.37 (1.27–1.49) Within 40 days: 1.56 (1.37–1.78) 40–79 days: 1.37 (1.19–1.59) 80–180 days: 1.27 (1.14–1.41)
Nonino et al. [118]	Cohort study	Provincial Dementia Registry of the Local Health Care Unit of Modena	Dementia patients >65 years ($N = 2,314$)	All-cause mortality	Incident use of AAPs vs. non-use	Mortality rate: AAP: 0.52/1,000 PY Non-use: 0.55/1,000 PY
Trifirò et al. [109]	Nested case–control study	Dutch Integrated Primary Care Information database, a general practice database	Dementia patients ≥65 years ($N = 2,385$)	All-cause mortality	Current use of AAP or CAP (non-use of respective class as comparator unless otherwise specified)	Adj. OR: Current use of AAP vs. current use of CAP: 1.3 (0.7–2.4) Current AAP use: 2.2 (1.3–2.9) Current CAP use: 1.7 (1.3–2.2)
Gill et al. [40]	Retrospective cohort study	Four administrative databases in Ontario: Ontario Drug Benefit program, Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan, Registered Persons Database	Dementia patients ≥66 years ($N = 27,259$)	All-cause mortality at 30, 60, 120 and 180 days after the initial dispensing of AP medication	Incident use of AAPs (non-use as comparator) and CAPs (AAP as comparator) stratified in CD, LTC cohorts	Adj. RR after 30 days of AAP vs. non-use: CD: 1.31 (1.02–1.70) LTC: 1.55 (1.15–2.07) Adj. RR after 30 days of CAP use: CD: 1.55 (1.19–2.02) LTC: 1.26 (1.04–1.53)
Schneeweiss et al. [36]	Retrospective cohort study	Linked administrative data from the British Columbia Ministry of Health, PharmaNet database and British Columbia	Patients ≥65 years with an AP prescription ($N = 37,241$)	180-day all-cause mortality	Incident use of AAPs and CAPs (risperidone as comparator)	Mortality rate: CAP: 14.1 % AAP: 9.6 % Adj. RR: Haloperidol: 2.14 (1.86–2.45) Loxapine: 1.29 (1.19–1.40) Olanzepine: 0.94 (0.80–1.09)
Kales et al. [37]	Retrospective cohort study	US Department of Veteran Affairs registries	Dementia patients ≥65 years with an AP prescription ($N = 10,615$)	1-year all-cause mortality from National Death Index	Incident use of AAPs, CAPs and combination of both types (CAP as comparator):	Mortality rate: AAP: 22.6 % CAP: 25.2 % Combination: 29.1 % Adj. RR: AAP: 0.93 (0.75–1.16) Combination: 1.33 (0.94–1.86)

Table 1 continued

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Hollis et al. [39]	Retrospective cohort study	Australian Department of Veteran Affairs claims-based pharmaceutical database	Veterans and war-widows ≥65 years ($N = 16,634$)	All-cause mortality	Incident use of antipsychotics, carbamazepine and valproate (incident use of olanzapine as comparator)	RR: Incident haloperidol use: 2.26 (2.08–2.47) Incident chlorpromazine use: 1.39 (1.15–1.67) Incident risperidone use: 1.23 (1.07–1.40)
Raivio et al. [51]	Cohort study	7 Finnish nursing homes and 2 hospitals	Frail elderly patients ($N = 254$)	All-cause mortality during a 2-year follow-up	Incident/prevalent use of AAPs and CAPs (non-use as comparator)	2-year mortality rate: AAPs: 32.1 % CAPs: 45.3 % Non-use: 49.6 % RR: AAPs: 0.49 (0.24–0.99) CAPs: 0.68 (0.46–1.03)
Hollis et al. [48]	Cohort study	Department of Veterans' Affairs database and Medicare Australia	Incident users of APs	All-cause mortality	CAPs (chlorpromazine, haloperidol, pericyazine, trifluoperazine), AAPs (quetiapine, olanzapine, risperidone) [olanzapine as comparator]	RR within 60 days: Chlorpromazine: 2.72 (1.84–4.01) Haloperidol: 2.17 (1.86–2.53)
Musicco et al. [119]	Retrospective cohort study	Milan Health information database	Patients ≥60 years prescribed an anticholinesterase inhibitor ($N = 4,369$)	All-cause mortality	AAPs or CAPs (no AP as comparator unless otherwise specified)	Adj. HR: CAPs: 3.7 (2.6–5.1) AAPs: 2.5 (2.0–3.0) CAPs vs. AAPs: 1.5 (1.1–2.1)
Aparasu et al. [49]	Retrospective cohort design matched on propensity score	Medicare and Medicaid data from Texas, Florida, New York and California	Nursing home residents ≥65 years ($N = 7,218$)	All-cause mortality	AAPs vs. CAPs (AAP as comparator)	Adj. HR: CAPs: 1.41 (1.27–1.57) <40 days after start of CAPs: 1.81 (1.49–2.18) 40–180 days after start of CAPs: 1.24 (1.09–1.42)
Kales et al. [42]	Retrospective cohort study	US Department of Veteran Affairs database	Dementia patients ≥65 years ($N = 1,932$)	180-day mortality	Risperidone, haloperidol, olanzapine, quetiapine (risperidone as comparator)	Propensity-weighted HR: Haloperidol: 1.57 (1.39–1.78) Olanzapine: 1.03 (0.92–1.16) Quetiapine: 0.74 (0.67–0.81)
Huybrechts et al. [41]	Cohort study	Linked data from Medicaid, Medicare, the Minimum Data Set, the National Death Index, and a national assessment of nursing home quality.	Nursing home patients ≥65 years ($N = 75,445$)	All-cause mortality (excluding cancer mortality) and cause-specific mortality	Incident use of haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone (risperidone as comparator)	Adj. HR for all non-cancer mortality: Haloperidol: 1.81 (1.65–1.98) Aripiprazole: 0.95 (0.78–1.15) Olanzapine: 1.01 (0.95–1.08) Quetiapine: 0.83 (0.77–0.89) Ziprasidone: 0.90 (0.69–1.17)

Table 1 continued

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Rafaniello et al. [107]	Prospective cohort study	Dementia Evaluation Unit of Campania	Dementia patients with BPSD ≥65 years who were incident antipsychotic users ($N = 1,618$)	All-cause-mortality	AAPs (non-use as comparator)	Rate per 100 PY: Quetiapine: 5.8 (4.4–7.7) Risperidone: 7.3 (4.8–11.1) Olanzapine: 4.6 (2.5–8.3) Clozapine: 7.7 (1.9–30.9) Aripiprazole: 17.6 (2.5–125.0)
Sultana et al. [43]	Retrospective cohort study	South London and Maudsley NHS Foundation Trust (SLaM) Biomedical Research Centre database, Clinical Record Interactive Search (CRIS)	Vascular dementia patients ($N = 1,531$)	All-cause mortality	AAPs (non-use as comparator)	Adj. HR: Prescription of olanzapine, quetiapine or risperidone ever: 1.05 (0.87–1.26) Quetiapine: 1.13 (0.92–1.37) Risperidone: 0.87 (0.60–1.27)

AAPs atypical antipsychotics, *Adj.* adjusted, *AP* antipsychotic, *BSPD* behavioural and psychological symptoms of dementia, *CAPs* conventional antipsychotics, *CD* community dwelling, *HR* hazard ratio, *LTC* long-term care, *NHS* National Health Service, *OR* odds ratio, *RR* relative risk, *PY* person years

similar alert was also later released by the manufacturer of aripiprazole [55].

Following the warning on antipsychotic-related stroke, several observational studies were conducted to compare the risk of stroke between atypical and conventional antipsychotics (Table 2). Most of these studies were conducted in an elderly population [50, 56–61] but only two were restricted to older patients with dementia [45, 62]. Risperidone and olanzapine were associated with a nearly threefold increase in the risk of CVEs in dementia patients [47, 63, 64]. The risk of CVE was extrapolated through the whole class of drugs, despite concerns that this was unjustified [21]. Four observational studies suggest a higher risk of stroke with atypical antipsychotics than with conventional antipsychotics, even in dementia [58, 65–67]. However, at least four studies found that the risk of CVE was higher for conventional agents than atypical agents [21, 68–70]. Although there is very limited data comparing the risk of individual drugs within the class of atypical or conventional antipsychotics, a difference in CVE risk has been reported between phenothiazines [RR 5.79 (3.07–10.9)] and butyrophenones [RR 3.55 (1.56–8.07)] as compared with other atypicals [RR 2.46 (1.07–5.65)] with respect to unexposed patients [60]. Another study reported that while conventional antipsychotics as a class were not associated with CVE, sulpiride was associated with CVE [71]. Similarly, as a class, atypical antipsychotics were slightly associated with CVE, while, by individual agent, quetiapine and risperidone were not [71]. Although this study suggests that the difference in risk between class and individual drugs may be important, the results of this study must be interpreted with caution because risk estimates were not statistically significant.

Limited data are available on the dose-effect relationship between antipsychotic dose and stroke [21], although a recently published study reported that higher antipsychotic doses are associated with higher risks of CVE [66]. It was, however, reported that with regards to the temporal relationship between dose and effect, an elevated risk was found during the first weeks of treatment, which decreases over time [72]. Another challenge of these studies was to identify unmeasured predictors of increased risk independently of drug use. In one study, users of olanzapine and risperidone with several vascular risk factors (which were either not adequately treated or completely untreated) were more likely to develop CVE, but it is unclear how much of this excess risk was due to the antipsychotics [73]. There can be additional methodological concerns about the diagnosis of CVE which may or may not be confirmed by radiological evidence. It is also not always clear how uniform or strict the definition of stroke or CVE employed across studies is, which may hinder direct comparison across studies.

Table 2 Observational studies investigating the risk of stroke due to antipsychotic use in dementia or elderly patients

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Herrmann et al. [56]	Retrospective cohort study	Administrative healthcare database in Ontario	Patients >65 years ($N = 11,400$)	Hospital admission due to stroke	Use of risperidone, olanzapine and CAPs (CAPs as comparator)	Adj. RR: Risperidone: 1.4 (0.7–2.8) Olanzapine: 1.1 (0.5–2.3)
Gill et al. [62]	Retrospective cohort study	Administrative healthcare database in Ontario	Patients ≥65 years with dementia ($N = 32,710$)	Hospital admission due to ischaemic stroke	New users of AAPs (risperidone, quetiapine and olanzapine) and CAPs (CAPs as comparator)	Adj. RR of AAPs vs. CAPs: 1.01 (0.81–1.26)
Liperoti et al. [45]	Case–control study	Nursing homes in Ohio, Maine, Illinois, Mississippi, South Dakota, and New York	Residents of nursing homes in six US states (Systematic Assessment of Geriatric drug use via Epidemiology database) with dementia ($N = 1,130$ cases and $N = 3,658$ controls)	Hospital admission for stroke or TIA	Current use of AAPs and CAPs (non-use as comparator)	Adj. OR: Risperidone: 0.87 (0.67–1.12) Olanzapine 1.32 (0.83–2.11) Other AAPs: 1.57 (0.65–3.82) CAPs: 1.24 (0.95–1.63)
Finkel et al. [57]	Retrospective cohort study	USA-wide Medicaid data	Dementia patients ($N = 18,987$)	New case of acute inpatient admission for CVE	Incident use of AAPs (risperidone, olanzapine, quetiapine and ziprasidone) and haloperidol (risperidone as comparator)	Adj. RR: Olanzapine: 1.05 (0.63–1.73) Quetiapine: 0.66 (0.23–1.87) Haloperidol: 1.91 (1.02–3.60)
Layton et al. [61]	Prescription event monitoring study	NHS UK prescription data as supplied by Prescription Pricing Authority	Patients of all ages, including patients with dementia ($N = 7,684$ patients on risperidone; $N = 8,826$ on olanzapine; $N = 1,726$ on quetiapine)	Any CVEs within first 180 days therapy	Incident use of risperidone, quetiapine and olanzapine (olanzapine as comparator)	Adj. RR: Risperidone: 1.2 (0.5–3.0) Quetiapine: 2.1 (0.6–7.7)
Percudani et al. [58]	Case–control study	Administrative healthcare database in Lombardy, Italy	Patients ≥65 years ($N = 35,604$)	Hospital admission due to any CVE	Previous use (as monotherapy) of AAPs (risperidone, olanzapine, quetiapine and clozapine) and CAPs (CAPs as comparator)	Adj. OR: CAPs vs. AAPs 1.42 (1.24–1.64)
Wang et al. [68]	Retrospective cohort study	The Pharmaceutical Assistance Contract for the Elderly Information from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) and Pennsylvania Medicare	Patients >65 years with at least one prescription for an antipsychotic ($N = 22,890$)	CVE	CAPs (AAPs as comparator)	Adj HR: 1.09 (1.02–1.16)
Barnett et al. [59]	Retrospective cohort study	Veteran Administration and Medicare database	Patients ≥65 years with dementia ($N = 14,029$)	Hospital admission due to any CVE	Incident use of AAPs and CAPs (non-use as comparator)	Adj. RR: CAPs: 1.29 (0.48–3.47) AAPs: 1.20 (0.83–1.74)
Sacchetti et al. [60]	Retrospective cohort study	Health Search Database, an Italian general practice database	Patients ≥65 ($N = 74,162$)	First ever stroke	Incident use of AAPs, butyrophenones, phenothiazines, benzamides (non-use as comparator)	Adj. RR: AAPs: 2.46 (1.07–5.65) Butyrophenones: 3.55 (1.56–8.07) Phenothiazines: 5.79 (3.07–10.9) Benzamides: 2.2 (0.98–4.90)

Table 2 continued

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Setoguchi et al. [50]	Cohort study	Healthcare utilization database in community setting containing all British Columbia residents ≥65	New APs users ($N = 37,241$), of whom 4,337 had dementia	All-cause mortality and specific-cause mortality	AAPs and CAPs (AAPs as comparator)	Adj. HR for all non-cancer deaths: CAPs: 1.27 (1.18–1.37)
Douglas and Smeeth [65]	Self-controlled case series	UK-based electronic primary care records in the General Practice Research Database	All patients registered in GPRD with a recorded incident stroke and at least one prescription for any antipsychotic ($N = 6,790$)	Stroke	All antipsychotic drugs available in database (non-use as comparator)	RR: All APs: 1.73 (1.60–1.87) CAPs: 1.69 (1.55–1.84) AAPs: 2.32 (1.73–3.10) All APs in dementia patients: 3.50 (2.97–4.12) CAPs only in dementia patients: 3.26 (2.73–3.89) AAPs only in dementia patients: 5.86 (3.01–11.38)
Chan et al. [71]	Retrospective cohort study	Patients in the Department of Psychiatry of the Pamela Youde Nethersole Eastern Hospital, China	Patients ≥65 years diagnosed with Alzheimer's disease, vascular or mixed dementia with BPSD ($N = 1,741$)	CVE	All APs (non-use as comparator)	Adj. HR: CAPs: 0.96 (0.58–1.59) Haloperidol: 0.92 (0.53–1.60) Trifluoperazine: 0.79 (0.18–3.47) Sulpiride: 1.48 (0.69–3.18) AAPs: 1.04 (0.35–3.07) Quetiapine: 0.901 (0.12–6.93) Amisulpride: 7.60 (0.62–92.26) Risperidone: 0.42 (0.05–3.29) Olanzapine 5.22 (0.57–47.73)
Laredo et al. [69]	Case-control study	UK-based electronic primary care records in the General Practice Research Database	Patients ≥65 years within the database ($N = 26,885$)	CVE	CVE in users versus non-users of AAPs/CAPs (non-use as comparator unless otherwise specified)	Adj. OR Any AP: 0.96 (0.89–1.04) Only CAPs: 1.16 (1.07–1.27) Only AAPs: 0.62 (0.53–0.72) [AAPs as comparator]
Huybrechts et al. [67]	Cohort study	Medicaid, Medicare, Minimum Data Set and Online Survey Certification and Reporting data for patients from nursing homes in 45 US states	Medicaid-eligible residents ≥65 years who initiated antipsychotic treatment in nursing homes ($N = 83,959$)	Hospitalization for CVE (stroke/TIA), within 180 days of treatment initiation	AAPs (AAPs as comparator when comparing classes; risperidone as comparator when comparing individual APs)	Propensity-adj. HR: CAPs: 0.81 (0.65–1.01) Aripiprazole: 0.99 (0.72–1.35) Olanzapine: 0.94 (0.84–1.05) Quetiapine: 0.91 (0.80–1.03)
Wu et al. [66]	Case-crossover study	National Health Insurance Research Database (NHIRD), Taiwan	Patients ≥18 with incident stroke within NHIRD ($N = 14,584$)	Stroke	All APs available in database (CAPs as comparator)	Adj. OR: AAPs: 1.91 (1.67–2.18)

Table 2 continued

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Wang et al. [70]	Case–case–time–control design study	US Veterans Health Administration database	Patients ≥60 years with a diagnosis of stroke ($N = 511$)	Ischaemic stroke	All APs (non-use as comparator)	Adj. OR: 1.8 (1.7–1.9)
Liu et al. [120]	Cohort study	National Health Insurance Research Database (NHIRD), Taiwan in Taiwan	Dementia patients ≥65 years	Stroke	All APs (no AP use in dementia patients as comparator)	Adj. HR for AP use in dementia: 1.17 (1.01–1.40)
Shin et al. [110]	Case-crossover study	Korean Health Insurance Review and Assessment Service database	Patients >64 years	Stroke	Risperidone, quetiapine and olanzapine (non-exposure as comparator)	Adj. OR for outcome within 30 days of starting AP: AAP: 3.9 (3.3–4.6) Risperidone: 3.5 (2.9–4.2) Quetiapine: 2.7 (2.0–3.6) Olanzapine: 1.2 (0.7–2.0)

AAPs atypical antipsychotics, *APs* antipsychotics, *Adj.* adjusted, *BPSD* behavioural and psychological symptoms in dementia, *CAPs* conventional antipsychotics, *CVE* cerebrovascular events, *HR* hazard ratio, *NHS* National Health Service, *OR* odds ratio, *RR* risk ratio, *TIA* transient ischaemic attack

The mechanism behind antipsychotic-related stroke in dementia is unknown but has been linked to orthostatic hypotension, hyperprolactinaemia resulting in atherosclerosis, thromboembolic events and excessive sedation [73, 74]. Some antipsychotic agents are known to antagonize α-adrenergic receptors, which is a pathway for hypotension. Antipsychotic agents most likely to have a hypotensive effect are clozapine, quetiapine, risperidone and olanzapine in decreasing order, while haloperidol and ziprasidone were associated with the lowest risk of hypotension [21]. Atypical and conventional antipsychotics are both associated with venous thromboembolism (VTE) [see Sect. 3.5]. On the other hand, it has also been hypothesized that the extrapyramidal effects of antipsychotics, which lead to stiffness and sedation, may later give rise to venous stasis and/or dehydration, which could increase the risk of CVEs. Yet another putative mechanism is the thrombogenic effect due to hyperprolactinaemia, which can result in enhanced platelet reactivity [75].

Despite these suggested mechanisms, the association between stroke and antipsychotics was questioned because of the absence of a solid and proven biologically plausible explanation, in addition to uncertainty about the diagnostic accuracy of either transient ischaemic attack (TIA) or stroke in the trials considered. The causal relationship between stroke and antipsychotics was further questioned because patients were often affected by vascular dementia, which is itself associated with cerebrovascular risk. Cognitive impairment and stroke are very much related and older patients with Alzheimer's disease are more likely to die from cerebrovascular disease than non-demented elderly subjects [21]. Following the warnings on antipsychotic-related stroke, several observational studies were conducted to compare the risk of stroke between atypical and conventional antipsychotics. Most of these studies were conducted in elderly populations [50, 56–61], but only two were restricted to older patients with dementia [45, 62]. The study by Gill et al. reported that long-term-care resident status was a risk factor for CVE [RR 1.15 (0.82–1.6)] for atypical antipsychotics, compared to conventional antipsychotics, as was a history of atrial fibrillation factor [RR 1.23 (0.70–2.02)] [62]. This study did not investigate the differential risk associated with antipsychotic use and provided no information on the duration or dose of antipsychotics used. Liperoti et al. reported the dose only descriptively without investigating the association between different doses and risk of CVE, although they provided risk estimates for the hospitalization of elderly nursing home residents with a diagnosis of stroke or TIA for two specific atypical antipsychotics: risperidone versus no use [odds ratio (OR) 0.87 (0.67–1.12)] and olanzapine versus no use [OR 1.32 (0.83–2.11)] [45]. Liperoti et al. also found that a history of CVE was an effect modifier for atypical

Table 3 Observational studies investigating the risk of pneumonia associated with antipsychotic use in dementia or the elderly

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Trifirò et al. [77]	Nested case–control	Dutch general practice database (Integrated Primary Care Information)	Patients (≥65 years) newly treated with antipsychotics ($N = 258$)	Fatal and non-fatal community-acquired pneumonia	AAPs or CAPs (past use of any AP as comparator)	Adj. OR fatal/non-fatal pneumonia: AAPs: 2.61 (1.5–4.6) CAPs: 1.8 (1.2–2.5) Fatal pneumonia: AAPs: 6.0 (1.5–24.0) CAPs: 1.7 (0.8–3.9)
Knol et al. [76]	Nest case–control	Dutch PHARMO database	Patients (≥65 years) newly treated with antipsychotics ($N = 22{,}944$; $n = 543$ cases)	Hospital admission due to pneumonia	AAPs or CAPs (non-use as comparator)	Adj. OR: Current use of AAPs: 3.1 (1.9–5.1) Current use of CAPs: 1.5 (1.2–1.9)
Gau et al. [121]	Case–control study	Rural community hospital in Ohio (US)	Patients aged ≥65 ($N = 194$)	Hospital admission due to community-acquired pneumonia	AAPs (non-use as comparator)	Adj. OR: AAP: 2.26 (1.23–4.15)
Star et al. [122]	Self-controlled cohort	UK Intercontinental Medical Statistics Health Disease Analyzer database	Adults aged ≥65 (number of patients not provided)	Acute chest infections, bronchopneumonia, hypostatic pneumonia	Distribution over time of AAPs and CAPs with respect to date of diagnosis of the study outcomes	In elderly patients (≥65 years): Higher rate of acute chest infections following AAPs and much less CAPs: Higher rate of bronchopneumonia following either AAP or CAP prescriptions
Barnett et al. [59]	Retrospective cohort study	US Veterans Administration database	Patients hospitalized due to pneumonia ($N = 16{,}931$)	In-hospital mortality	AAPs or CAPs (no use of neuropsychiatric drugs as comparator)	Adj. OR: CAPs: 1.5 (1.0–2.2) AAPs: 1.2 (1.0–1.5)
Hatta et al. [111]	Prospective observational study	33 general hospitals, where at least one psychiatrist worked full time	Patients who developed delirium during hospital admission and received antipsychotics for delirium ($N = 2{,}453$, of which 30 % had dementia)	Serious adverse events including aspiration pneumonia	All APs prescribed	Aspiration pneumonia [*n* (%)]: With all APs, 17 (0.7) With risperidone, 7 (0.8) With quetiapine, 4 (0.5) With perospirone, 0 (0) With olanzapine, 2 (2.3) With aripiprazole, 0 (0) With haloperidol, 3 (0.6) With 'other' antipsychotics, 1 (0.8)

AAPs atypical antipsychotics, *Adj.* adjusted, *APs* antipsychotics, *CAPs* conventional antipsychotics, *OR* odds ratio

Table 4 Observational studies investigating the risk of other adverse events associated with antipsychotic use in dementia or elderly persons

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Hip or femur fracture						
Liperoti et al. [112]	Case–control study	Systematic Assessment of Geriatric drug use via Epidemiology database	Nursing home residents in six US states	Hospitalization for hip fracture; hospitalization for hip fracture ICD-9 820–821	CAPs as a class, haloperidol, other conventional agents; AAPs as a class, risperidone, olanzapine, other atypical agents (non-use as comparator)	OR hospitalization for hip fracture: CAP: 1.35 (1.06–1.71) Haloperidol: 1.53 (1.18–2.26) Hospitalization for hip fracture ICD-9 820–821: AAPs: 1.37 (1.11–1.69) Risperidone:1.42 (1.12–1.80) Olanzapine: 1.34 (0.87–2.07)
Kolanowski et al. [123]	Case–control study	Health claims database	Health care insured dementia patients aged >70 years ($N = 959$)	Diagnosis of hip fracture	AAPs or CAPs (non-use as comparator)	OR: AAPs: 1.47 (0.82–2.65) CAPs: 2.33 (1.08–5.03)
Pouwels et al. [113]	Case–control study	Dutch PHARMO database	Patients >18 years with a hip/femur fracture during the study period ($N = 6{,}763$ cases; $N = 26{,}341$ controls)	Hospitalization for hip fracture	AAPs and CAPs (non-use as comparator)	Adj. OR CAPs: 1.76 (1.48, 2.08) Pipamperone: 1.54 (1.15–2.06) Haloperidol: 2.33 (1.72–3.18) Zuclopenthixol: 2.44 (1.59–3.75) Thioridazine: 1.51 (0.60–3.78) Levomepomazine: 0.80 (0.35–1.82) Others: 1.19 (0.79–1.78) AAPs: 0.83 (0.42–1.65) Risperidone: 0.84 (0.38–1.88) Quetiapine, olanzapine, clozapine: 0.83 (0.23–3.02)
Jalbert et al. [124]	Case–control study	Nursing homes in California, Florida, Illinois, New York, and Ohio	Long stay, Medicaid-eligible residents age >65 years living in nursing homes with at least 20 beds ($N = 764$ cases; $N = 3{,}582$)	Hospitalization for hip fracture, ICD-9 820 Hospitalization for hip fracture	AAPs and CAPs (non-use as comparator)	Adj. OR: Incident use of AAPs: 1.36 (0.95–1.94) Prevalent use of AAPs: 1.33 (1.08–1.63) Prevalent use of CAPs: 1.28 (0.7–2.34)
Pratt et al. [125]	Self-controlled case series study	Australian Government Department of Veterans' Affairs Health Care Claims Database	Veterans/spouses aged ≥65 years hospitalized for hip fracture ($N = 8{,}285$)	Hospitalization for hip fracture ICD-10 S720, S721	CAPs (non-use as comparator)	IRR: 1 week: 1.04 (0.40–2.70) 2–8 weeks: 2.2 (1.65–3.02) 9–12 weeks: 1.79 (1.12–2.84) >12 weeks: 2.19 (1.62–2.95)
Wang et al. [126]	Case–control study	Medicare, New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled administrative database	Patients ≥65 years ($N = 1{,}222$ cases: $N = 4{,}888$ controls)	Hospitalization for hip fracture ICD-10 S720, S721 (non-hip fracture patients as comparators)	Any AP use	Adj. OR for any AP use: 1.60 (p-value 0.0001)
Deep vein thrombosis						

Table 4 continued

Study	Study design	Setting	Population	Outcome	Exposure	Main findings
Schmedt and Garbe [101]	Nested case–control study	German Pharmacoepidemiological Research Database	Dementia patients >65 years	Hospitalization with a main discharge diagnosis for DVT (ICD-10-GM codes I80.1, I80.2, I80.3) or PE (ICD-10-CM code I26.x).	CAPs and AAPs (non-use as comparator)	Adj. OR: Current AP use 1.23 (1.01–1.50) Prevalent AP use: 1.09 (0.87–1.36) Incident AP use: 1.63 (1.10-2.40) Past user: 0.75 (0.53–1.05) AAPs: 0.89 (0.64–1.24) CAPs: 0.94 (0.74–1.20) All APs: 1.62 (1.15–2.27)
Hyperglycaemia						
Lipscombe et al. [106]	Nested case–control study	Four administrative databases in Ontario: Ontario Drug Benefit database, National Ambulatory Care Reporting System database, Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan	Diabetic patients ≥66 ($N = 13{,}817$)	Occurrence of hyperglycaemia		Adj. RR for patients treated with insulin: Any current AP: 1.40 (1.06–1.85) Incident AP use: 15.4 (8.12–29.2) Prevalent AP use: 1.36 (1.03–1.79) AAP use: 1.4 (1.06–1.85) Incident AAP use: 16 (8.26–31.1) Prevalent AAP use: 1.38 (1.04–1.82) CAP use: 1.27 (0.75–2.12) Incident CAP use: 11.6 (4.75–28.3) Prevalent CAP use: 1.01 (0.52–1.98) Adj. RR for patients treated with oral hypoglycaemic agents: Any current AP use: 1.36 (1.12–1.66) Incident AP use: 14.4 (8.71–23.8) Prevalent AP use: 1.31 (1.08–1.60) AAP use: 1.37 (1.12–1.67) Incident AAP use: 15.4 (9.08–26.0) Prevalent AAP use: 1.35 (1.10–1.64) CAP: 1.31 (0.90–1.90) Incident CAP use: 11.7 (5.81–23.4) Prevalent CAP use: 0.95 (0.58–1.57)

AAPs atypical antipsychotics, *adj.* adjusted, *APs* antipsychotics, *CAPs* conventional antipsychotics, *DVT* deep vein thrombosis, *ICD* International Classification of Diseases, *ICD-10-CM* ICD-10-Clinical Modification, *ICD-10-GM* ICD-10-German Modification, *IRR* incidence rate ratio, *NHs* nursing homes, *OR* odds ratio, *PE* pulmonary embolism, *RR* risk ratio

antipsychotic use [RR 4.63 (1.35–32.63)], in particular for olanzapine use [RR 3.71 (1.55–8.84)] and, to a lesser degree, for risperidone [RR 1.49 (0.93–2.38)]. However, no other antipsychotics were considered individually, whether atypical or conventional [45].

3.3 Pneumonia

Infections, primarily pneumonia, have been listed as one of the most prevalent causes of death among elderly demented patients using antipsychotics, both in clinical trials and observational studies [21] (Table 3). It is difficult to explore the relationship between antipsychotics and pneumonia since patients with dementia already have a higher risk of aspiration pneumonia, which makes any observational study liable to confounding by indication. Moreover, frail older patients may initially manifest pneumonia with delirium, requiring antipsychotic drug treatment, thus also raising the potential for protopathic bias in observational studies [76]. A Dutch study investigating the association between the hospital-based diagnosis of pneumonia and antipsychotic use reported a threefold increased risk during use of atypical antipsychotics and 1.6-fold increase during use of conventional antipsychotics as compared with non-use in an elderly population [76]. Setoguchi et al. [50] found a slightly higher rate of fatal pneumonia during conventional antipsychotic use relative to atypical antipsychotic use, but the overall risk of antipsychotic linked to the use was not increased compared with non-use in a cohort of elderly patients. Trifirò et al. [77] showed that the use of either atypical or conventional antipsychotics in elderly patients is associated with an increase in the risk of pneumonia in a dose-dependent manner. Looking at individual agents, Trifirò et al. found the highest risk of pneumonia was associated with risperidone [OR 3.51 (1.94–6.36)], followed by zuclopenthixol [OR 2.25 (1.00–5.08)], haloperidol [OR 1.95 (1.20–3.17)], olanzapine [OR 1.90 (0.61–5.90)] and paliperidone [OR 1.55 (1.00–2.43)]. Given the frequency and poor prognosis of pneumonia in elderly dementia patients, it is important to explore the relationship between the use of each single antipsychotic and pneumonia in dementia patients. To our knowledge, this has only been explored by one study, a recently published study which found that, using risperidone as comparator, olanzapine and ziprasidone had a stronger association with pneumonia than quetiapine and aripiprazole; this study was, however, limited by the small numbers of ziprasidone and aripiprazole users [67].

The possible mechanisms of antipsychotic-induced pneumonia remain speculative. It is likely that antipsychotics may induce aspiration pneumonia in dementia patients through many possible mechanisms involving extrapyramidal adverse events, dysphagia, or sedation, as a result of modulation of dopamine, cholinergic, and H_1-histaminergic receptors, respectively [78]. Due to differences in the receptor-binding profiles among various antipsychotics, the risk of pneumonia for any single antipsychotic and the underlying mechanism should be further investigated. In one study, it has already been shown that the risk of pneumonia is differential between atypical [OR 5.97 (1.49–23.98)] and conventional antipsychotics [OR 1.71 (0.76–3.87)], between subclasses such as butyrophenones [OR 1.42 (0.59–3.37)] and other antipsychotics such as thioxanthene, diphenylbutylpiperidine, and benzamide derivatives [OR 2.84 (0.74–10.92)], as well as between some individual antipsychotics (see above) [78]. However, this study only considered five antipsychotics individually, leaving doubts about the risk associated with other antipsychotics. In addition, methodological issues such as confounding by indication and protopathic bias obscure the association between antipsychotic drugs and pneumonia, and their effect on risk estimates must be considered thoroughly in order to avoid misleading results [78].

3.4 Cardiac Arrhythmias

Sudden cardiac death associated with conventional antipsychotic use has been reported since the early 1960s, mostly for haloperidol and thioridazine [79]. Particular attention has been paid to antipsychotic drugs' potential to prolong the QTc interval, which may result in Torsade de pointes and other potentially fatal ventricular arrhythmias [80]. QTc interval prolongation was reported to be highest for thioridazine, sertindole, pimozide, haloperidol, quetiapine and ziprasidone, in decreasing order [81]. Several observational studies have confirmed the signals from spontaneous reports, suggesting that conventional antipsychotics are associated with an increased risk of SCD [79, 82–84]. In particular, thioridazine was withdrawn from the market in some countries due to concerns of cardiac arrhythmia [85]. Recently, two large US studies found that the risk of SCD is also increased with the four most frequently prescribed atypical antipsychotics (clozapine, olanzapine, quetiapine and risperidone) [44, 82, 84]. On the basis of this evidence, electrocardiography monitoring would be prudent in routine clinical care if antipsychotics are prescribed to elderly patients [86, 87]. No studies investigated arrhythmogenic potential of antipsychotics in patients with dementia, specifically, and none of the currently available studies had the statistical power to look at dose and duration effects of individual drugs on SCD risk.

3.5 Peripheral Vascular Effects

Antipsychotic use has been associated with the occurrence of VTE, an association that was recently reviewed by the

UK Medicines and Healthcare products Regulatory Agency (MHRA) [88]. A relationship between antipsychotic medications and VTE was first suggested around five decades ago [88]. However, despite early descriptions and subsequent reports of VTE associated with antipsychotic use, evidence for a true link has not been clearly established. Reviews of the available data for aripiprazole, clozapine and olanzapine have led to warnings about VTE being added to their Summaries of Product Characteristics (SPCs) [88]. There are now several studies on VTE and antipsychotics [84, 89–100], mostly on young patients with schizophrenia and with methodological limitations (small sample size, inadequate control of confounding). Findings about specific drugs were inconsistent, but all studies concluded that an increased risk of VTE with atypical and/or conventional antipsychotics was likely [88]. Very little data are available on the peripheral vascular effects of antipsychotics in dementia, which is highly relevant given the extensive use of other potentially interacting medications acting on serotonin receptors and platelet function in these patients. To our knowledge, only one study investigating the link between antipsychotic use and VTE has been published, a recent nested case–control study using a cohort of 72,591 dementia patients [101]. This study found that among users of antipsychotics from this population, current users had a statistically significant increased risk of VTE [OR 1.23 (1.01–1.60)] compared with controls, defined as dementia patients at risk of VTE. Within the subgroup of current antipsychotic users, new users had a higher risk of VTE than controls, than prevalent users or past users. The risk of VTE did not appear to vary between first- and second-generation antipsychotics when these were analysed as separate groups; the risk of VTE associated with individual antipsychotics was not investigated [101]. No other studies investigated the differential risk of VTE associated with individual antipsychotics.

3.6 Metabolic Effects

While mortality, stroke and pneumonia were the main focus of research, several other adverse events related to antipsychotic use are also a source of concern (Table 4). Metabolic effects of antipsychotics are a long-term safety concern and may contribute to further increase the cardiovascular risk in older people with dementia [102]. In patients with either schizophrenia or bipolar disorder, the use of antipsychotics (i.e. olanzapine, clozapine) has been associated with metabolic abnormalities, including weight gain, lipid disturbances and altered glucose homeostasis [103]. Whether elderly patients with BPSD receiving antipsychotics develop similar disturbances is still unclear. Metabolic effects of antipsychotics in elderly patients with dementia are difficult to assess in general as food intake is reduced in these subjects. Only a few and relatively small studies have been published so far on this association. Rondanelli et al. [104] concluded, on the basis of 36 nursing home residents with Alzheimer's disease, that treatment with low-dose atypical antipsychotics does not lead to weight gain or increase in the risk of type II diabetes or lipid metabolism abnormalities. In contrast, the CATIE-AD trial reported weight gain during the use of olanzapine, quetiapine and risperidone in 421 Alzheimer's disease patients, and the risk increased over time [105]. Beside an increase in body weight, there was no apparent effect on glucose levels, total cholesterol and triglycerides levels, apart from an unfavourable change in high-density lipoprotein cholesterol and girth with olanzapine. Post hoc analyses of other studies with olanzapine and risperidone were consistent with the CATIE-AD trial [21]. A recently published Canadian study by Lipscombe et al. [106], carried out using four administrative databases in Ontario, found that among older patients with diabetes, the initiation of treatment with antipsychotic drugs was associated with an increased risk hyperglycaemia.

The risk of hyperglycaemia appeared to be much higher for incident use [RR 15.4 (8.12–29.2)] than prevalent antipsychotic use [RR 1.36 (1.03–1.79)] for insulin-treated patients taking any antipsychotic, and slightly higher for atypical antipsychotic use [RR 1.4 (1.06–1.85)] than for conventional antipsychotic use [RR 1.27 (0.75–2.12)] among these patients. The overall risk of hyperglycaemia was slightly lower when patients were prescribed oral hypoglycaemic agents and were incident antipsychotic users [RR 14.4 (8.71–23.8)] compared with when they were prescribed insulin. However, Lipscombe et al. [106] did not investigate the risk of hyperglycaemia associated with individual antipsychotics and this remains unknown at present. Presently, the association between antipsychotic use and either hyperglycaemia in elderly diabetic patients with dementia or new-onset diabetes in elderly dementia patients requires better investigation [21]. In addition, it should be clarified if such possible metabolic effects (i.e. hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia and weight gain) of antipsychotics lead to a clinically relevant increased risk of all-cause mortality in these patients over the period of antipsychotic treatment in dementia patients

4 Directions for Future Research on Antipsychotics in Behavioural and Psychological Symptoms of Dementia

The body of scientific evidence regarding the safety and efficacy of antipsychotics in BPSD is expanding; however, there are several significant research gaps that still exist. There are very limited data on the safety of individual

antipsychotics, as illustrated above. In addition, most antipsychotic safety studies tend to group all BPSD patients together rather than evaluating outcomes by individual BPSD symptoms. Only one study has investigated an outcome (mortality) considering symptoms such as delirium and hallucinations in dementia patients prescribed antipsychotics [107]. The type of dementia associated with BPSD is also likely to influence the safety of antipsychotics, but this has been a somewhat neglected area of clinical research.

So far, comprehensive safety data about long-term use of antipsychotics in dementia patients in various settings and different European countries is missing [108]. Although various clinical trials and observational studies have investigated the postmarketing risk of all-cause mortality [35–37, 40, 43, 44, 51, 109], cerebrovascular adverse events [45, 50, 56–62], SCD [79, 80, 82–84], VTE/pulmonary embolism [88–99], diabetes mellitus and other metabolic effects [76, 102–105], and community-acquired pneumonia [76–78] associated with atypical and conventional antipsychotics, few of these studies were able to properly assess the short- and long-term risk for each single antipsychotic separately in a well-powered study, despite emerging evidence that their clinical characteristics seem to be different. Of the 16 mortality studies we considered in this review, only six investigated the risk of some individual antipsychotics [36, 37, 41–43, 48]; of the 18 stroke studies, only seven investigated individual antipsychotics [45, 56, 57, 61, 67, 71, 110]. Only one of six studies investigated the risk of pneumonia with individual antipsychotics [111]; only two of six studies investigated the risk of hip fracture with individual antipsychotics [112, 113], and neither of the studies investigating the risk of deep vein thrombosis and hyperglycaemia evaluated the individual risk of antipsychotics. This missing information could have important implications for choosing the drug with least risk in populations particularly prone to specific adverse drug reactions (ADRs). The optimal dose associated with the least risk of various ADRs is also not well-investigated with regards to antipsychotic use in BPSD, a potentially important aspect of antipsychotic safety given that the dose of antipsychotics in BPSD is lower than that in schizophrenia or bipolar disease. This is particularly relevant given the pharmacokinetic and pharmacodynamic characteristics of dementia patients. Most observational studies were focused on elderly populations rather than elderly dementia patients specifically. Moreover, these studies were conducted in a specific region or country (mostly the US), which restricts heterogeneity in exposure, thus resulting in a lack of statistical power to evaluate the entire range of individual antipsychotics and prevent generalizability of the findings to dementia patients from other countries. For instance, results from US observational studies can hardly be generalized to the European setting due to the differences about the prescribing pattern of antipsychotics in dementia between the US and Europe.

Individual RCTs were powered on efficacy outcomes and could not provide useful insights on safety outcomes. In addition, systematic reviews and meta-analyses of randomized data were not able to disentangle the absolute and relative risk of each antipsychotic versus placebo and versus other antipsychotics. For some newer atypical antipsychotics, findings have not been systematically reviewed yet. Furthermore, the safety of antipsychotics in BPSD is rarely compared with other off-label medications, such that the risks cannot be compared with other therapeutic options.

The long-term safety of antipsychotics in BPSD in particular presents a critical limitation in BPSD research so far as there is very limited evidence of any benefit of these drugs for the treatment of BPSD over periods longer than 12 weeks. Most dementia patients discontinue antipsychotic treatment after a few weeks, yet a relevant proportion of them take these drugs for much longer periods. The AGIT and DART studies did not demonstrate any advantage for antipsychotics compared with placebo over 6 months [114–117], and the CATIE study described no overall benefit [17]. However, the CATIE trial did indicate that antipsychotics were less likely to be discontinued because of perceived ineffectiveness over 9 months than placebo [17]. Furthermore, there are very limited data comparing antipsychotics with other off-label drugs in BPSD and, similarly, limited data on the withdrawal of individual antipsychotic agents.

5 Conclusions

There are few observational studies that report the risk of adverse events with individual antipsychotics in elderly dementia patients. The highest risk of mortality was reported for haloperidol [36, 39] and chlorpromazine [48], while the lowest risk was reported for olanzapine [36], quetiapine [41, 42] and ziprasidone [41]. The evidence is much less clear-cut for stroke, with some studies reporting an increased [56, 61] or decreased [45, 67, 71, 110] risk with risperidone, increased [61, 110] or decreased [57, 71] risk with quetiapine, and increased [57] or decreased [110] risk with haloperidol. Only one study investigated the risk of pneumonia with individual antipsychotics but this did not provide a risk estimate nor was it sufficiently powered [111]. The risk of fracture was highest for zuclopenthixol [113] and haloperidol [112, 113], although too few studies investigated this outcome for these results to be conclusive. Only one study investigated DVT [101] and hyperglycaemia [106], neither of which considered the individual risk of antipsychotics.

While research on antipsychotic efficacy and safety in BPSD has expanded, research on the efficacy of individual antipsychotics in specific BPSD symptoms and the safety issues of individual antipsychotic use in BPSD has lagged behind. There are several studies suggesting a difference between the safety profile of atypical and conventional antipsychotics but there are only a few studies on individual antipsychotic safety, suggesting that inter-drug differences in this respect are indeed being overlooked.

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