Mortality risk from long-term treatment with antipsychotic polypharmacy vs monotherapy among adults with schizophrenia spectrum disorder: a systematic review and meta-analysis of observational studies

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Abstract

Background: Long-term use of more than one concurrent antipsychotic [antipsychotic polypharmacy (APP)] is widely believed to contribute to excess mortality in people with serious mental illness (SMI) compared to those taking one antipsychotic (monotherapy). However, no conclusive evidence is available.

Methods: We conducted a systematic search in 6 major electronic databases from inception until December 2019, identifying observational studies examining the association between mortality and exposure to long-term APP vs monotherapy. Studies were eligible if they adopted a follow-up design and antipsychotic exposure was >3 months among adults with SMI. We determined the pooled mortality risk using random-effects meta-analyses. The review was registered in PROSPERO (CRD42019148044).

Results: A total of 12 studies fulfilled all eligibility criteria reporting quantitative data for 834, 534 person years. No difference was found in the association between all-cause mortality and APP vs monotherapy use, in both crude (rate ratio=0.94, 95% CI 0.81–1.10, p=0.446; I^2=83.2%, p<0.001; 10 studies) and adjusted models (adjusted HR=0.98, 95% CI 0.80–1.19, p=0.802; I^2=58.3%, p<0.05; 5 studies). Meta-regression did not identify any moderators influencing all-cause mortality risk. For natural causes of death, risk estimates followed the same pattern: (i) crude rate ratio=0.88, 95% CI 0.67–1.14, p=0.324; I^2=77.7%, p=0.01 (5 studies); (ii) adjusted HR=1.04, 95% CI 0.90–1.99, p=0.590; I^2=0.0%, p=0.744 (5 studies).

Conclusion: Mortality risk of APP use in people with SMI appears to be comparable to that of monotherapy use, although work to date remains heterogeneous, precluding firm conclusions from made. Complex real-world clinical scenarios may be contributing to this lack of variation between these two types of antipsychotic use.

Key words: mortality; antipsychotics; polypharmacy; risk; schizophrenia; meta-analysis; serious mental illness

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1.0 BACKGROUND

Epidemiological findings consistently demonstrate elevated mortality rates among adults with serious mental illness (SMI), traditionally defined as schizophrenia-spectrum disorders, bipolar disorders and other non-organic psychotic disorders, compared with the general population (2020; Chang *et al*., 2011; Buhagiar *et al*.). Long-term antipsychotic use has been historically implicated to be a major contributor to this excess mortality due to the associated cardiometabolic adverse effects (Weinmann *et al*., 2009). Recent robust evidence from nationwide cohorts, however, points towards an opposite direction, indicating reduced all-cause mortality among patients with SMI using long-term antipsychotics compared with those not using any (Vermuelen *et al*., 2017; Taipale *et al*., 2018; Tiihonen *et al*., 2009; Tiihonen *et al*., 2019). Adequate antipsychotic treatment may thus have a net beneficial effect on improving general well-being and social functioning, compensating for potential cardiometabolic adversities impacting on longevity (Tiihonen *et al*., 2009).

The benefit and safety of long-term use of more than one concurrent antipsychotic [antipsychotic polypharmacy, (APP)] relative to a single antipsychotic (monotherapy), yet remains more contentious (Kasteridis *et al*., 2019). Existing practice guidelines, including those for schizophrenia and related psychotic disorders, advise against long-term APP use due to assumptions about limited efficacy and risk of excess mortality compared to monotherapy (Lehman *et al*., 2004; Royal College of Psychiatrists, 2014). Despite these reservations, long-term treatment with APP for resistant psychotic symptoms when monotherapy has failed, is believed to be a valid therapeutic approach in real-world clinical practice (Faries *et al*., 2005; Correll *et al*., 2009; Gallego *et al*., 2012). Evidence related to mortality risks in these guidelines is notably based on early small studies conducted among homogenous populations (Waddington *et al*., 1998; Joukamaa *et al*., 2006), with methodological shortcomings and limited generalisability (Kadra *et al*., 2018). Consequently, strict adherence to these guidelines based on sparse evidence regarding mortality, implies that a sub-group of patients with SMI may experience worse overall clinical outcomes despite their symptoms meriting treatment with APP when all other recognised strategies to address refractory symptoms, [e.g. clozapine initiation (Kadra *et al*., 2018; Kasteridis *et al*., 2019) or adjunctive electroconvulsive therapy (ECT) (Petrides *et al*., 2015)], have failed.

Emerging evidence from large studies with rigorous designs has latterly challenged such assumptions about the limitations of APP (Tiihonen *et al*., 2019). Firstly, large observational studies have demonstrated lower hospitalisation and emergency department presentation rates in people using APP compared to those using monotherapy (Katona *et al*., 2014; Kasteridis *et al*., 2019; Tiihonen *et al*., 2019). Secondly, evidence from population-based registry studies with advanced methodologies has also started to mount, questioning the elevated mortality risks linked with APP use (Baandrup *et al*., 2010; Katona *et al*., 2014; Kasteridis *et al*, 2019). A large cohort study in Hungary found even lower mortality rates associated with APP relative to monotherapy (Katona *et al*., 2014). A similar study in South London reported equivocal outcomes, identifying reduced survival associated with APP relative to monotherapy in statistical models adjusted for participant-level variables and proportion of recommended antipsychotic dose, but no difference when modelled on participant-level variables only (Kadra *et al*., 2018). Therefore, overall there is to date heterogeneous evidence on the mortality risks of long-term APP use and no firm conclusions can be derived.

Long-term APP is used in at least 30% of patients with SMI, the majority of whom have a lifelong illness (Gallego *et al*., 2012). Given the widespread use of APP in maintenance treatment and ensuing warnings deterring such APP use, knowledge related to mortality outcomes from long-term APP load is germane to determining treatment choices. We therefore conducted a systematic review with meta-analyses, aiming to address the following research question: *does long-term APP use affect the risk of mortality relative to monotherapy use in adults with SMI?*

2.0 MATERIALS AND METHODS

The review closely adhered to the MOOSE proposal (Stroup *et al*., 2000) and PRISMA statement (Moher *et al*., 2009]. A protocol was published and registered in the PROSPERO database before commencement of the full search and analysis (registration code CRD42019148044 available from: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=148044).

2.1 Data sources

We searched British Nursing Index, CINAHL, EMBASE, EMCare, MEDLINE and PsycINFO without language restrictions since their inception through to 31st December 2019. Additional searches were conducted by means of manual screening of the reference lists of the included studies and relevant

key papers, as well as Google Scholar, to ensure both forward- and backward-tracking of literature sources.

2.2 Search strategy

A search strategy was developed combining the following keywords, including MeSH subheadings, for "serious mental illness" or "schizophrenia" and "antipsychotics" and "mortality". The full search strategy is presented in supplementary Table S1.

2.3 Study selection

We included longitudinal observational studies of any design according to the following pre-defined inclusion criteria: The study (i) included adult participants aged 16 years and above ; (ii) contained a majority of participants diagnosed with SMI, including schizophrenia and related disorders, bipolar disorder and other non-organic psychotic disorders, established by any diagnostic criteria; (iii) compared participants using two or more antipsychotics relative to those using antipsychotic monotherapy as a primary or secondary objective of the study, or presented data allowing comparative statistical inferences to be computed between the two different types of antipsychotic use; (iv) exposure to antipsychotics was at least 3 months; (v) reported mortality data (all-cause or specific) as mortality rates or risk estimates summarised as odds ratios (OR), relative risks (RR) or hazard ratios (HR) and corresponding 95% confidence intervals (95% CI), or presented data regarding mortality that allowed manual calculation of crude risk estimates.

Studies were excluded if they (i) only included participants who were older than 65 years; (ii) involved cohorts treated with antipsychotics that could not be defined as having SMI, such as personality disorders and dementia; (iii) reported duplicate outcomes; (iv) lacked a comparison group of participants using monotherapy and (v) adopted a controlled trial design with or without randomisation. The latter studies were excluded as these were envisaged *a priori* not to have examined long-term APP use. Furthermore, a robust meta-analysis reporting mortality outcomes associated with short-term APP has already been conducted (Schneider-Thoma *et al*., 2018).

2.4 Data extraction

The titles and abstracts of the retrieved studies were assessed for eligibility by two authors (GT and KB) and any discrepancy was resolved by discussion and consensus with the last author (DG). Once a study met eligibility criteria for final inclusion, data were extracted and entered into a database. The

following study-level variables were extracted: first author's name, publication year, country, study design, period of data collection, years of follow-up or person years of antipsychotic exposure, specific psychiatric diagnoses, mean age of participants at inclusion, source of participants and methods or source of ascertainment of death. Estimate-level variables included the following: number of total participants and deaths in comparison (APP) and reference (monotherapy) groups, number of deaths (all-cause or from specific causes when available) from either group and confounders if reported. When required, corresponding authors were contacted in order to ensure completeness or clarification of data. Risk of bias of individual studies was evaluated using the Newcastle-Ottawa scale (Wells *et al*., 2000), rated independently by two authors and discrepancies addressed in accordance with the same principles for determining study eligibility.

2.5 Statistical analysis

Analysis was conducted in *Stata* version 16 for Windows (StataCorp, Texas, USA) using the user-written *admetan* commands for meta-analysis (Fisher, 2018).

We conducted separate meta-analyses for all-cause mortality, natural causes of death and unnatural causes of death loosely adopted from principles employed in a previous meta-analysis examining the mortality associated with antipsychotic use relative to no use (Vermuelen *et al*., 2017). As we anticipated significant heterogeneity across different studies at the outset, we used the DerSimonian and Laird random-effects model (DerSimonian and Lard, 1986) for all meta-analyses and to generate corresponding Forest plots. The reference group in both summary and pooled outcomes was monotherapy use.

(1) For all eligible studies, including those that did not specifically analyse and/or report mortality data for APP vs monotherapy use, we first calculated the crude mortality rates per 1000 person years for participants receiving APP or monotherapy if these were not reported, using the formula: person years = [(number of participants at risk at baseline + number of participants at end-point)/2] x (number of years in the time interval) (Szklo and Nieto, 2014]. We then used these data to generate crude mortality rate ratios and corresponding 95% CI for each study, to finally calculate a pooled estimate of the crude mortality rate ratio with 95% CI.

(2) For studies analysing time-to-event data using Cox proportional hazard models, we used the reported adjusted HR (aHR) and 95% CI. If more than one multivariable model was reported, we used data for the model reporting the risk estimate for the longest duration of antipsychotic exposure and adjusted for most confounders. If aHRs were not explicitly available, we used other summary statistics or data extracted from Kaplan-Meier survival curves to estimate the aHR and corresponding 95% CI using the methods described by Tierney *et al*. [2007]. If more than one

analysis was reported based on the number of antipsychotics comprising APP, we first combined results using a fixed effects model and included the ensuing pooled result in the overall analysis. The two eligible case-control studies investigating mortality from natural causes (Baandrup *et al*., 2010; Chen *et al*., 2019) reported their risk estimate as adjusted odds ratio (aOR) as correctly expected from the study design. In this instance, we first converted the aOR to adjusted relative risk (aRR) using the methods outlined by Wang (2013), making the debatable assumption that OR is a surrogate measure for RR. Subsequently we made a further debatable assumption that RR and HR are broadly equal statistics for short time frames (Stare and Maucort-Boulch, 2016). We finally calculated pooled estimates of the aHR with 95% CI for the three types of mortality outcomes.

Statistical heterogeneity across eligible studies was assessed using the χ^2-based Cochran's *Q* and Higgins's I^2 indices. To assess the degree of potential publication bias, Egger's regression test was applied and funnel plots were generated. Suspected factors contributing to heterogeneity and potential bias were also investigated using meta-regression models, namely: decade of publication (≤2010 or not), sample size (*n*=≤300 or not) and duration of antipsychotic exposure (continuous variable) for analyses with at least ten studies (Thompson & Higgins, 2002). Influence analyses were also conducted by omitting one study at a time in succession for all meta-analyses in order to determine whether the results were markedly altered by a specific single study. Statistical significance was set at an alpha level of 5% throughout.

3.0 RESULTS

3.1 Study selection

The systematic search yielded initially 4,910 unique citations, with 13 published studies conducted among adult participants were meeting our eligibility criteria (Fig 1). One study (Montout *et al*., 2002) did not have sufficient data for inclusion in the quantitative synthesis, only reporting outcomes of interest in a single free-text sentence with no numeric data. The original dataset was no longer available from the authors (personal communication). This study was therefore excluded from onward quantitative synthesis.

[Insert Fig. 1 here]

3.2 Description of studies

The characteristics of the included studies are summarised in Table 1. In total, the 12 studies reporting quantitative data reported mortality outcomes for a total of 834, 534 person years, with a mean age of inclusion of 46.2 (±6.5) years and mean exposure to antipsychotics for 6.1 (±4.9) years on average. Studies were all conducted during the past two decades, and all but one in European countries, which was conducted in China (Chen *et al*., 2009). While all studies included participants with schizophrenia and related disorders, two studies also included a smaller proportion of participants with bipolar disorder (Kadra *et al*., 2018: 20.3%; Kasteridis *et al*., 2019: 31%). Two studies utilised a population-based nested case-control design (Baandrup *et al*., 2010; Chen *et al*., 2019). Of these, the study by Baandrup *et al*. (2000) was the index study addressing the mortality associated with APP vs monotherapy as a primary aim, while that by Chen *et al*. (2019) pursued an essentially identical methodology to the latter. The three earliest studies adopted a prospective cohort design using case note data (Montout *et al*., 2002; Morgan *et al*., 2003; Joukamaa *et al*., 2006). The rest of the studies had a retrospective cohort design, mostly using epidemiological (Tiihonen *et al*., 2009; Tiihonen *et al*., 2012; Kadra *et al*., 2018; Taipale *et al*., 2018; Kasteridis *et al*., 2019; Tiihonen *et al*., 2019) or health insurance databases (Tenback *et al*., 2012; Katona *et al*., 2014). Five studies (Morgan *et al*., 2003; Joukamaa *et al*., 2006, Tenback *et al*., 2012; Taipale *et al*., 2018; Tiihonen *et al*., 2019) primarily reported mortality associated with APP vs no antipsychotic use, although sufficient data were available in the publication or from the authors to derive crude mortality estimates associated with APP vs monotherapy use.

[Insert Table 1 here]

The seminal registry-based Finnish studies (Tiihonen *et al*., 2009; Tiihonen *et al*., 2012; Tiihonen *et al*., 2019) used the same population across the three studies, covering increasingly longer observation periods, each with unique features: (i) in the first of these studies, perphenazine was the chosen monotherapy in order to allow comparisons with the CATIE study (Lieberman *et al*., 2005); (ii) a later study presented separate outcomes according to whether antipsychotics were combined with either antidepressants or benzodiazepines; (iii) the most recent study specifically analysed hospitalisation rates associated with polypharmacy vs monotherapy, but data related to all-cause mortality were presented in the supplementary material as a secondary objective.

Quality of the studies was uniformly high, with all attaining scores of either 8 or 9 on the Newcastle-Ottawa scale, although two studies (Morgan *et al*., 2003; Joukamaa *et al*., 2006) had notably small sample sizes (see Supplementary Table S2).

3.3 Mortality

The 12 studies conducting quantitative analysis reported a total of 5,724 deaths during 397,262 person-years in participants using APP, as opposed to 8,141 deaths during 437,272 person-years in those using monotherapy. All studies adjusted for potential confounders in their multivariable models. Five studies (Tenback *et al*., 2012; Katona *et al*., 2014; Taipale *et al*., 2018; Kasteridis *et al*., 2019; Tiihonen *et al*., 2019) only reported all-cause mortality outcomes, without distinguishing between natural and unnatural deaths, whereas two studies reported risk estimates for deaths from natural causes only (Baandrup *et al*., 2010; Chen *et al*., 2019). Five studies reported data according to specific antipsychotics among participants using monotherapy (Tiihonen *et al*., 2009; Tenback *et al*., 2012; Katona *et al*. 2014; Taipale *et al*., 2018; Tiihonen 2019), although in one study (Tiihonen *et al*., 2009), only perphenazine was the reference group for adjusted outcomes. Only two studies described the actual constitution of APP, providing different aHRs for various antipsychotic combinations (Katona *et al*., 2014; Tiihonen *et al*., 2019). One study was unique in reporting final models adjusting separately for either olanzapine-equivalent doses or percentage of maximum recommended doses in the British National Formulary (Kadra *et al*., 2018). Extracted or derived crude mortality rates per 1000 person-years associated with APP or monotherapy use are presented in Supplementary Table S3. A summary of the main findings from all eligible studies is provided in Supplementary Table S4.

3.5 Unadjusted risk estimates for polypharmacy versus monotherapy use

Forest plots for unadjusted risk estimates for mortality are shown in Fig. 2. The pooled results with a random effects model showed no variation between the unadjusted all-cause mortality rates associated with long-term APP use compared to monotherapy use. The pooled all-cause mortality rate ratio was 0.94 (95% CI 0.81–1.10, p=0.446; 10 studies), but heterogeneity was significantly high (Q=53.58; I^2=83.2%, p<0.001). Influence analyses by means of sequential exclusion of one study did not alter the results (rate ratio range=0.93 to 0.99). In univariable meta-regression, the comparative all-cause mortality risk estimate between the two types of antipsychotic use was not associated with any of the variables of interest (decade of publication, p=0.721; sample size, p=0.328; duration of exposure, p=0.205). After accounting for all of these potential moderator variables in a multivariable regression, residual variation due to heterogeneity remained high (I^2=86.2%, p<0.001). Egger's test did not suggest any significant publication bias (p=0.203) (also see funnel plot, supplementary Fig. S2).

Five studies reported sufficient data to compute pooled crude ratio for deaths from natural causes, revealing a similar outcome: rate ratio=0.88, 95% CI 0.67–1.14, p=0.324; Q=17.9; I^2=77.7%, p=0.01.

Egger's test did not suggest significant publication bias (p=0.330) (also see funnel plot, supplementary Fig. S3).

There was insufficient data in the studies to calculate the risk estimate for deaths from unnatural cause.

[Insert Fig. 2 here)

3.6 Adjusted risk estimates for polypharmacy versus monotherapy use

Random effects meta-analysis of the fully adjusted hazard ratios for all-cause mortality reported in the five eligible studies showed no difference in the risk of death associated with long-term APP use relative to monotherapy use (aHR=0.98, 95% CI 0.80–1.19, p=0.802; Q=9.60; I^2=58.3%, p<0.05) (see Forest plot, Fig. 3A; funnel plot, supplementary Fig. S4). Influence analysis did not alter the results (aHR range=0.91–1.08). A similar pattern of results was obtained for pooled adjusted risk estimates for death from (i) natural causes (pooled aHR=1.04, 95% CI 0.90–1.99, p=0.590; Q=1.96; I^2=0.0%, p=0.744; influence analysis, aHR range=0.98 to 1.09; 5 studies) (see Forest plot, Fig. 3B; funnel plot, supplementary Fig. S5), and (ii) unnatural causes (pooled aHR=0.92; 95% CI 0.69–1.24, p=0.580; Q=0.51; I^2=0.0%, p=0.776; 3 studies) (see Forest plot, supplementary Fig. S6).

[Insert Fig. 3 here)

4.0 DISCUSSION

In this study we quantitatively summarised 12 eligible studies evaluating directly or indirectly mortality outcomes associated with long-term APP use (as opposed to APP due to cross-titration or switching) relative to monotherapy use in people with SMI. Methodologically, it builds on a previous quantitative synthesis on antipsychotic-associated mortality (Vermeulen *et al*., 2017), but is unique in specifically addressing mortality risk associated with long-term APP use vs monotherapy use, an area which remains contentious to date. Results revealed comparable mortality outcomes between the two types of antipsychotic use in both adjusted and unadjusted models, irrespective of the cause of mortality (i.e. all-cause mortality, mortality from natural causes and mortality from unnatural causes). Meta-regression and influence analyses, did not identify any moderators or unique studies affecting these results, respectively.

Long-term APP use has been generally considered to be associated with higher risk of mortality, outweighing any clinical advantage over monotherapy, as also reflected by the strong reservations for its use in contemporary treatment guidelines for SMI (Correll *et al*., 2010; Kasteridis *et al*., 2019). Our pooled quantitative results, on the other hand, are not entirely in line with these earlier considerations. However, findings from our meta-analysis in this respect need to be interpreted with significant reservations. First, is the context of the usual pitfalls associated with pooling significantly heterogeneous observational studies from electronic research databases, including: marked variation in the recording of epidemiological and prescribing data, divergent methodologies of the included studies, inconsistent definition of APP constitution, dose and length of exposure, as well as discrepancies in regional clinical practice and ensuing trends of APP use. Second, as indicated by the Forest plots of our analyses of unadjusted rate ratios for all-cause mortality (Fig. 1; Fig S1), there was an approximately equal number of studies favouring lower risk for either type of antipsychotic use. The same issue was also present with pooled analyses of aHRs, this being further compounded by the even smaller number of included studies (five). Our pooled results indicating mortality risk estimates approaching 1.0 in all instances are therefore not surprising. Consequently, findings from the current study should neither represent absolute proof for lack of higher mortality risk associated with APP relative to monotherapy as previously assumed, nor should they be interpreted to advocate routine and liberal APP use in clinical practice. In other words, our findings clearly fall short of providing absolute resolution to the debate surrounding the controversies surrounding APP use. Instead, they are intended to yield a foundation for the direction of research, so that future work exploring these comparative mortality risks can be fine-tuned to overcome the lack of clear-cut findings arising from unintentional shortcomings of research to date.

However, earlier findings pointing a positive association between long-term APP use and mortality, were supported by two consistently cited observational studies carried out two decades ago using case records: (i) Waddington *et al*. (1998) reported outcomes based on a small sample of participants (*n*=88) from a rural area in Ireland followed up for ten years, which may not be generalisable to the wider population; (ii) Joukamaa *et al*. (2006), analysed a sub-sample (*n*=99) from a much larger cohort study in Finland followed up for 17 years. Both studies adopted similar statistical approaches using regression models evaluating the cumulative relative effect of the number of concurrently prescribed antipsychotics compared to none, but the results of the actual direct comparisons between APP vs monotherapy use was not reported. In addition, the antipsychotic regimes were obtained at baseline rather than at the time of death many years later, hence the associations reported in these studies may not necessarily reflect the true temporal association between antipsychotic use and death. Using data reported in Joukamaa *et al*. (2006), our

estimate of crude all-cause mortality outcomes, in actual fact reveal a statistically insignificant variation in the unadjusted risk between the two types of antipsychotic use (2 antipsychotics vs monotherapy, crude RR =1.24, 95% CI 0.68-2.28, *p*=0.482; ≥3 antipsychotics vs monotherapy, crude RR=1.61, 95% CI 0.84-2.11, *p*=0.155). One further study (Morgan *et al*., 2003) conducted by the same research group in Ireland, adopted similar statistical models from a small cohort of participants from the same geographical area spanning a different time frame. However, their results showed no predictive effect for the number of concurrent antipsychotics on survival, consistent with the overall trend obtained from our meta-analyses. Findings from our meta-analyses, together with earlier work of Tiihonen *et al*. (2009; 2012; 2019) may therefore be timely in driving future work to elucidate the unresolved conundrum.

Several seminal studies have consistently demonstrated the reduced risk of mortality related to long-term antipsychotic use in general compared to no use (Crump *et al*., 2013; Kiviniemi *et al*., 2013; Tiihonen *et al*., 2009). This advantage may stem from the improved mental state and social functioning derived from adequate treatment of psychosis, in turn leading to improved lifestyle choices mitigating the adverse cardiometabolic effects inherent to antipsychotics (Taipale *et al*., 2018). In real-world settings, treatment concordance among patients with SMI is yet generally poor (Tiihonen *et al*., 2011). One plausible explanation for the lack of difference in the risk between APP vs monotherapy, could therefore be that patients with prescriptions for two antipsychotics or more, may be more likely to take at least one of them. It is also possible that in practice, patients may not actually take the full prescribed dose of APP, instead titrating it on their own accord based on their tolerability. This discrepancy was in fact identified in the study by Tiihonen *et al*. (2019), where total consumed doses of some APP combinations were indeed lower than the defined equivalent dose of monotherapy. Therefore, despite that patients prescribed add-on APP, on average are likely to be more symptomatic than those receiving monotherapy and have been prescribed higher combined daily dose equivalence than monotherapy (Katona *et al*., 2014), they may prefer to take multiple antipsychotics at lower doses than those prescribed. Evidence suggests that combinations of certain antipsychotics may increase antipsychotic action and/or reduce side-effect burden due to interactions with different receptors (Galling et al., 2017), leading to improved symptom control and treatment adherence respectively. Improved symptomatic control following APP even at lower combined doses, may then generate compensatory mechanisms for metabolic syndrome and poor social functioning in a similar fashion to that operating in those receiving monotherapy relative to no use. Consequently, this counteracts the assumed excess mortality risk that is otherwise more likely to arise from the high-dose antipsychotic prescribing usually associated with APP (Roh *et al*., 2014).

4.2 Methodological considerations

One limitation of the current study was the deliberate choice to exclude RCTs from our synthesis. Given the enduring nature of SMI, outcomes associated with antipsychotic treatment evolve over a number of years, which are unlikely to be captured by short-term RCTs. In addition, RCTs may be underpowered to find any meaningful difference in mortality during their course, given that it would require thousands of person years for this to be measured meaningfully. A preliminary search prior to retrieval of eligible studies, in fact did not indicate the presence of RCTs evaluating APP-associated mortality for longer than 3 months. A recent meta-analysis on antipsychotic-related mortality specifically including RCTs, additionally did not reveal elevated risk associated with short-term APP use (<3 months) compared to monotherapy (Schneider-Thoma *et al*., 2018). Finally, evidence related to efficacy of treatment obtained from RCTs is unlikely to inform the range of treatment decisions needed for the complexities encountered in real-world clinical scenarios among people with SMI (Ballon and Stroup, 2013). On the other hand, the majority of the observational studies included in the current study utilised large electronic epidemiological databases providing long observation periods with a large amount person years, minimising selection bias associated with observational studies and allowing the cumulative effect of antipsychotics to develop, directing findings towards effectiveness.

One eligible study was particularly unique in showing about a 40% lower risk of mortality associated with APP compared with monotherapy (Katona et al., 2014). However, its methodology is likely to have been prone to selection bias as previously also noted by other authors (Kadra *et al*., 2018 Tiihonen *et al*., 2019), predisposing to a degree of residual confounding even in the adjusted risk estimates. Other large-scale observational studies have partly addressed this limitation by employing various approaches, including calculations of the status of current medication use at each time point, and entered discontinued APP use as a covariate in multivariable analyses (Tiihonen et al., 2012; Taipale et al., 2018; Tiihonen et al., 2019). On the other hand, some other studies did not adjust for confounders more commonly found in people with more severe forms of the SMI and who are more likely to be APP relative to those with milder forms treated effectively with monotherapy. Consequently, this might have overinflated APP mortality risk. Regardless of the complexity and refinement of the statistical methods employed in these studies, residual and unmeasured confounding in therefore unlikely to have been completely addressed, and while this is an inherent issue with complex observational studies (Fewell *et al*., 2007), it does not entirely eliminate the shortcomings of RCTs noted above. This might have therefore, further added to the somewhat not clear-cut implications of our findings. Our sequential leave-one-out analysis, yet, did not alter our

results, suggesting that risk estimates form individual studies irrespective of their outlying risk estimate findings, might not have significantly affected our pooled risk estimates overall.

Another significant limitation is the inconsistent definition of APP across the included studies. While some studies used complex and robust algorithms to extract these data [(e.g. Kadra et al., 2018, as detailed in separate sister paper (Kadra et al., 2015)], other studies employed more straightforward approaches to the definition of APP (e.g. Baandrup *et al*., 2010 and Chen *et al*., 2019: at least one filled prescription for APP in the 90 days prior to death). Owing to the nature of the datasets in the included studies, some of these studies were also unable to determine the actual antipsychotic regimen immediately prior to death (i.e. whether APP or monotherapy). In addition, while studies with complex designs adjusted for time-varying covariates (e.g. switch from monotherapy to APP and vice versa) (Tiihonen *et al*., 2019), the majority of studies did not have relevant data to account for alterations to prescribing during the time leading to death. There was no straightforward approach to address these variations as moderating effects in our meta-regression due to intrinsic heterogeneities, hence these significant issues need to be borne in mind when drawing conclusions.

Studies generally pooled results for groups of SMI diagnoses. One study (Katona *et al*. 2014) reporting a sensitivity analyses of the core group of participants with schizophrenia only, revealed unchanged results relative to the main findings among participants with other SMI diagnoses. Potentially this infers that the overall findings from the current analysis may be relevant to the range of disorders constituting SMI. As treatment with APP is widespread across other disorders such as dementia and personality disorders (Grech and Taylor, 201) the implications of our findings are yet beyond the scope of these other groups of disorders.

One study identified marked differences in mortality risk associated with different combinations of antipsychotics compared to no use, with some being associated with either lower or higher risk relative to monotherapy (Tiihonen *et al*., 2019). Despite these differences, we used a fixed-effects model to pool the reported outcomes into a single risk estimate for all APP combinations, although this was nevertheless essential in order to institute homogenisation with the rest of the eligible studies.

A large proportion of studies reported outcomes on all-cause mortality, without differentiating their analyses between natural and unnatural deaths, which are likely to have varying aetiological underlying contributors. However, deaths from unnatural causes usually constituted a much smaller proportion than that of deaths caused by natural causes, and those individual studies reporting such outcomes separately did not find any difference in outcomes (e.g. Kadra *et al*., 2018:

all-cause mortality, aHR=1.2; natural death, aHR=1.2; unnatural death=1.1; all statistically insignificant).

All of the eligible studies were conducted in high-income developed countries, and all but one study was based in Europe (the other being from a single large province in China). The results may therefore not necessarily be applicable to other societies, with non-white or less so, non-Asian majority populations.

Strengths of this review include the *a priori* published protocol in PROSPERO, with a comprehensive search strategy, independent screening of studies and assessment of risk of bias, and the subsidiary sensitivity analyses to test the robustness of findings. In general, there was a low risk of bias with the primary studies due to their thorough design. Finally, the majority of primary studies were conducted on nationwide cohorts based on real-world clinical data, ultimately increasing their external validity.

4.3 Implications of findings and future directions of research

While our findings suggest an absence of differential mortality risk between APP and monotherapy use, the following crucial clinical caveats that necessitate to be borne in mind, amidst the overarching controversies surrounding APP use. First, patients receiving APP are more likely to be severely ill than those receiving only monotherapy (Grech and Taylor, 2012). Subsequently they are more likely to receive higher combined doses of antipsychotics as also highlighted by one of the primary studies (Kadra *et al*., 2018). In turn this predisposes to higher risk of severe adverse effects in general and ultimately increases the risk of diminished concordance (Langan and Shajahan, 2010; Lochmann van Bennekom *et al*., 2013). Second, a guiding principle in pharmacological treatment is that once an ideal dose of antipsychotic is reached (whether monotherapy or APP), introducing additional treatments or doses may add little benefit to clinical response (Lochmann van Bennekom *et al*., 2013). Third, clozapine monotherapy remains the most effective antipsychotic drug, which itself is associated with the lowest odds of mortality compared to no use and to other monotherapies (Tiihonen *et al*., 2009). Nevertheless, as identified by the findings of one the primary studies, APP is often prescribed in favour of clozapine monotherapy (Kadra *et al*., 2018), and clozapine initiation is itself often unnecessarily delayed by a number of years (Howes *et al*., 2012). Fourth, adjunctive ECT could also be a viable option in the treatment of SMI in instances when clozapine monotherapy has failed, as evidenced by a recent RCT (Petrides *et al.*, 2015).

Notwithstanding this, emerging evidence from observational studies suggests that APP in its own right may still be feasible when all other treatments have failed. The largest such study to date

found that certain APP combinations are associated with lower rates of readmission to hospital for both somatic and psychiatric indications, whereas others may have insignificant effects (e.g. risperidone with aripiprazole) and some may even have more adverse outcomes (e.g. aripiprazole with quetiapine for somatic hospitalisation only) (Tiihonen *et al*., 2019). Different antipsychotics targeting different receptor profiles may thus be beneficially combined to improve clinical outcomes if selected judiciously, perhaps at doses lower than that of monotherapy itself, in instances when monotherapy is insufficient to control symptoms.

These findings related to APP treatment outcomes, mirror the trends regarding differential mortality rates associated with specific long-term APP combinations relative to no use and to monotherapy (Tiihonen *et al*., 2019). In addition, the study by Kadra et al. (2018) uniquely demonstrated the significant implications of dose equivalence (i.e. expressed in relation to chlorpromazine or otherwise) with respect to APP-associated mortality risks. Considerations of these two latter factors have to be made, in furtherance to addressing the unique antipsychotic combinations in concurrent treatment. This may add strength to the postulated basis of the receptor profile targeted by APP in reducing symptoms and ensuing risk of death. Most notably is that the highest reductions in mortality as well as rehospitalisation risks appear to be associated with APP combinations involving clozapine (Tiihonen *et al*., 2019). This may infer that clozapine-associated APP may be very different from non-clozapine APP. While this was only specifically investigated by the most recent study (Tiihonen et al., 2019), it may yet bear key implications on the future understanding of APP mortality risks.

Against the backdrop of the evidence highlighted by our review, future epidemiological studies on antipsychotic-associated mortality would benefit from analysing mortality outcomes based on specific APP combinations rather than pooling data irrespective of the constitution of APP. Distinguishing between clozapine-related APP and other forms of APP would also be crucial. Dose equivalence need to be entered consistently as confounding variables in statistical models, as this was not the case with some studies to date and observed outcomes in the primary observational studies are likely to have been unable to account for a range of unmeasured confounding. Standardising the definition of APP in future studies could also reduce inconsistency of reporting and outcomes. Exploring associations with specific underlying causes of death is also likely to be beneficial in elucidating the finer details of these associations. Finally, the effectiveness of long-term APP use in SMI, should be explored in longer-term RCTs, albeit acknowledging that this may be a particularly challenging and potentially unfeasible endeavour.

In conclusion, our study is the first of its kind to quantitatively summarise and synthesise primary observational studies addressing the risk of mortality associated with long-term APP use vs monotherapy use in adults with SMI. Combined results of both crude and adjusted risk estimates indicate no difference in mortality rates of people treated with long-term APP use relative to monotherapy, even after accounting for moderating and influencing factors. However, conclusions from our findings are not entirely clear-cut. In real-world scenarios, various complex mechanisms may be operating that mitigate the previously assumed risk of excess mortality from APP, such as specific antipsychotic combinations or patients consuming lower APP doses than those intended by their prescribers. At clinical and policy levels, these findings, nevertheless, may drive the need to reappraise the warnings to date against maintenance treatment with APP in all clinical scenarios.

Funding source: This study did not receive specific funding.

Contributors: KB, DG and GT devised the conceptual design of the study. KB and GT selected the studies, assessed study quality and extracted data. KB wrote the first draft of the manuscript, performed the statistical analysis and data interpretation. DG, GT, HB and MD provided further critical input to data interpretation and to later drafts. All authors approved the final version of the manuscript. KB and DG are the guarantors.

Declaration of competing interests: We declare no competing interests.

Acknowledgements: We thank Dr. Giouliana Kadra, Prof. Nicholas Moore, Prof Stefan Priebe, Dr. Heidi Taipale and Prof. Jari Tiihonen for providing feedback and/or additional unpublished data for the study.

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