The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial

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Summary

Background Data from 12-week placebo-controlled trials have led to mounting concerns about increased mortality in patients with Alzheimer's disease (AD) who are prescribed antipsychotics; however, there are no mortality data from long-term placebo-controlled trials. We aimed to assess whether continued treatment with antipsychotics in people with AD is associated with an increased risk of mortality.

Methods Between October, 2001, and December, 2004, patients with AD who resided in care facilities in the UK were enrolled into a randomised, placebo-controlled, parallel, two-group treatment discontinuation trial. Participants were randomly assigned to continue with their antipsychotic treatment (thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone) for 12 months or to switch their medication to an oral placebo. The primary outcome was mortality at 12 months. An additional follow-up telephone assessment was done to establish whether each participant was still alive 24 months after the enrolment of the last participant (range 24–54 months). Causes of death were obtained from death certificates. Analysis was by intention to treat (ITT) and modified intention to treat (mITT). This trial is registered with the Cochrane Central Registry of Controlled Trials/National Research Register, number ISRCTN33368770.

Findings 165 patients were randomised (83 to continue antipsychotic treatment and 82 to placebo), of whom 128 (78%) started treatment (64 continued with their treatment and 64 received placebo). There was a reduction in survival in the patients who continued to receive antipsychotics compared with those who received placebo. Cumulative probability of survival during the 12 months was 70% (95% CI 58–80%) in the continue treatment group versus 77% (64–85%) in the placebo group for the mITT population. Kaplan–Meier estimates of mortality for the whole study period showed a significantly increased risk of mortality for patients who were allocated to continue antipsychotic treatment compared with those allocated to placebo (mITT log rank p=0·03; ITT p=0·02). The hazard ratio for the mITT group was 0·58 (95% CI 0·35 to 0·95) and 0·58 (0·36 to 0·92) for the ITT population. The more pronounced differences between groups during periods of follow up longer than 12 months were evident at specific timepoints (24-month survival 46% *vs* 71%; 36-month survival 30% *vs* 59%).

Interpretation There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication; these results further highlight the need to seek less harmful alternatives for the long-term treatment of neuropsychiatric symptoms in these patients.

Funding UK Alzheimer's Research Trust.

Introduction

Worldwide, there are an estimated 25 million people with dementia,[1] most of whom have Alzheimer's disease (AD). AD is a devastating illness, which results in a progressive decline and distressing neuropsychiatric symptoms.[2–4] Antipsychotics are widely used as the first-line pharmacological approach to treat the neuropsychiatric symptoms of AD. The results of 24 placebo-controlled trials of typical or atypical antipsychotics have indicated a significant[5–7] but modest[8] improvement in aggressive behaviour compared with placebo over 6–12 weeks of treatment. The best evidence is for risperidone, for which five placebo-controlled trials have been published.[5] The results of the few studies that lasted for 6 months or longer suggest only modest[8] or no benefit[9,10] from longer therapy.

However, there is also clear evidence of a significant increase in adverse effects, including parkinsonism, sedation, oedema, chest infections, accelerated cognitive decline, and cerebrovascular events (odds ratios 2·5–3·0), in patients with AD who are treated with antipsychotics.[5,7,11] A recent meta-analysis suggested there was a significant increase in mortality risk (1·5–1·7 fold) during the 6–12 week period of treatment in randomised placebo-controlled trials.[12,13] On the basis of this information, the US Food and Drug Administration (FDA) published a warning about a significant increase in mortality risk with treatment with atypical antipsychotics in patients with AD.[12]

In many of the nursing homes in Europe and North America, up to 30–60% of residents with dementia are prescribed antipsychotics,[14–16] commonly for longer than a

Lancet Neurol 2009; 8: 151–57

Published Online January 9, 2009 DOI:10.1016/S1474-4422(08)70295-3

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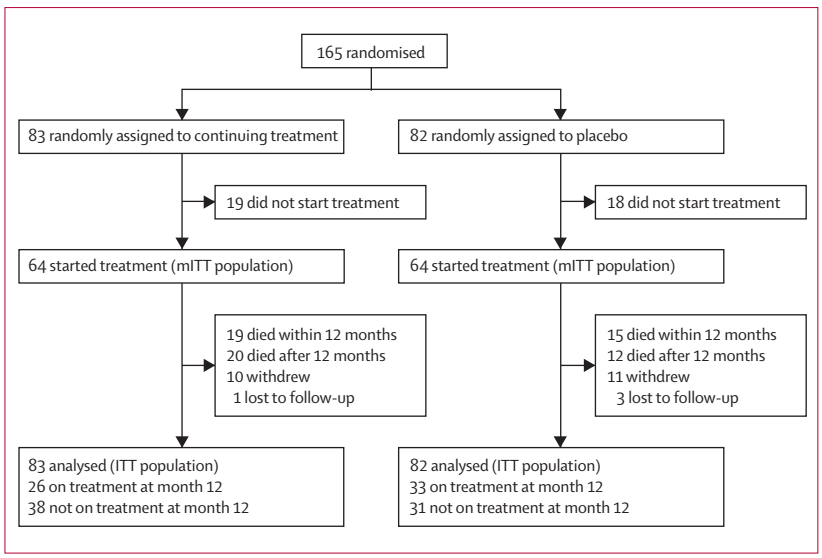

Figure 1: **Trial profile**

year.[17,18] This is problematic because the randomised clinical trials that reported increased mortality risk with antipsychotics lasted only between 4 and 14 weeks; however, in clinical practice, treatment is more often continued for longer periods. Schneider and colleagues[13] reported the absolute difference in risk of excess deaths as only 1% (with upper limits to the CI of 4% to 5%, depending on the drug) during 6–12 weeks. However, these questions remain: is the risk increased during treatment for more than 12 weeks; and do the raised ORs mean there is an increase in the absolute number of excess deaths in frailer people with AD who took antipsychotic maintenance treatment in nursing homes? There are several case register studies, most [19–21] but not all[22] of which indicate a significant but more modest association between long-term use of antipsychotics and increased mortality in older people. However, most of these studies are difficult to interpret because the data do not enable the separate evaluation of people with dementia, although Hollis and colleagues[19] did confirm the increased mortality risk associated with antipsychotics in a subgroup of people who took cholinesterase inhibitors.[19] Additionally, because the information in the case register series is not based on data from randomised trials, there is a potential for bias from the association of neuropsychiatric symptoms with poor prognosis.[23] Therefore, randomised trials of longer duration are needed to determine the relation between long-term use of antipsychotics and mortality in patients with Alzheimer's disease. Owing to the reported association between antipsychotics and cerebrovascular events in people with dementia, it is also important to ascertain whether there is an excess of cerebrovascular deaths with prolonged antipsychotic use.

We have reported the results of a 12-month randomised, placebo-controlled antipsychotic withdrawal trial to establish whether continued treatment with antipsychotics had a significant effect on cognition or neuropsychiatric symptoms.[10] In light of emerging evidence from meta-analyses of excess mortality,[5,12,13] we were also able to compare mortality between people with Alzheimer's disease who took antipsychotics or placebo over 1 year in this randomised controlled trial, and to collect additional follow-up data for up to 54 months, to assess long-term differences in mortality. By use of these data we now hope to answer an important question: is continued treatment with antipsychotics in patients with dementia associated with a persistent risk of increased mortality?

Methods

Patients

We enrolled patients with dementia due to AD who resided in care facilities in four areas of the UK (Oxfordshire, Newcastle and Gateshead, London, and Edinburgh) and who were prescribed the antipsychotics thioridazine, chlorpromazine, haloperidol, trifluoperazine, or risperidone for behavioural or psychiatric disturbance for at least 3 months. These specific drugs were selected because they were the antipsychotics most commonly prescribed to people with dementia in the UK, according to national prescribing data at the start of the study. Inclusion criteria were: living in a nursing or residential home; fulfilling the NINCDS/ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) criteria for possible or probable AD; a mini-mental state examination (MMSE) score higher than 6 points or a severe impairment battery (SIB) score higher than 30 points; taking at least 10 mg chlorpromazine equivalents of an antipsychotic drug or 0·5 mg/day risperidone. Exclusion criteria were: inability to complete primary outcome measures at baseline assessment; any physical condition—including marked extrapyramidal disorder—that would have made participation in the trial distressing or likely to increase suffering; taking thioridazine and showing a prolonged QT interval corrected for heart rate on electrocardiogram (ECG);[24] or inability to take capsules.

This study was approved by a human research ethics committee under the rules of the UK National Research Ethics Service. Written consent was given by all study participants who had sufficient capacity. If individual participants did not have the capacity to give consent, written assent was provided by the next of kin in accordance with the requirements of the research ethics committee and UK law at the time of the study.

Procedures

Initial randomisation was done centrally at the Centre for Statistics in Medicine in Oxford (CSM), by use of dedicated computer software (MINIM, version 1.5 [a randomisation program for allocating patients to treatment in clinical trials]). The randomisation

programme included a minimisation algorithm to ensure the balanced allocation of participants across the intervention groups for the following prognostic factors: presence or absence of extrapyramidal signs (EPS), visual hallucinations and delusions, use of cholinesterase inhibitors, MMSE score higher or lower than 6 points, and current typical or atypical antipsychotic medication. To avoid predictability, the first 22 patients were allocated randomly without the minimisation factors. The minimisation algorithm was applied to subsequent patients with an allocation ratio that was not fully deterministic. The statistician who did the randomisation had no direct contact with patients; therefore, the allocation was totally independent of patient recruitment.

Detailed methods for the design and the cognitive and neuropsychiatric outcomes of this randomised controlled trial have already been published.[10] Patients randomised to active treatment received a dose of antipsychotic that was as close as possible to the one they were already receiving. Details of the dose regimen have been reported.[10] Patients were treated with either very low, low, or high doses of antipsychotic to best match the clinically prescribed dose before trial entry (risperidone [0·5 mg once a day, 0·5 mg twice a day, 1 mg twice a day]; chlorpromazine [12·5 mg once a day, 12·5 mg twice a day, 25 mg twice a day]; trifluoperazine [0·5 mg once a day, 0·5 mg twice a day, 1 mg twice a day]; haloperidol [0·75 mg once a day, 0·75 mg twice a day, 1·5 mg twice a day]) or placebo in capsules that matched those in the very low, low, or high dose regimens, so that each participant either continued their antipsychotic treatment or was randomised to placebo. Each antipsychotic was over-encapsulated to maintain the double-blind design. Placebo capsules were identical to the over-encapsulated antipsychotics, but contained just inert filler. Antipsychotic or placebo treatments were maintained at the same fixed dose throughout the 12-month treatment period. The primary outcome of the trial was mortality at 12 months. Additional follow up was completed for a minimum of 2 years after initial enrolment (range 24–54 months) for individual participants, to determine the long-term effect on mortality of continuing or discontinuing antipsychotics. The months of follow up reported refer to each patient from the first assessment (month 0) to a particular assessment point (ie, time from month 0 to the specific follow-up assessment).

Telephone assessments were done to establish whether a participant was still alive 24 months after the enrolment of the last participant (range of follow-up period 24–54 months) up to April, 2006. The primary assessment of mortality was based on these interview data, but for each deceased participant we attempted to obtain the death certificate to provide additional information on the date and, in particular, the cause of death. CB, RJ, and RMcS, blinded to the original treatment assignment, each made an independent determination of whether any of the stipulated causes of death were possibly or probably related or were unrelated to cerebrovascular disease. Discrepancies were resolved by consensus discussion.

	Continue treatment (n=83)	Placebo (n=82)
Women	64 (77%)	62 (76%)
Age (years)	84·8 (7·0), 68·3–100·2	84·9 (6·1), 67·0–100·6
Substantial EPS	39 (47%)	39 (48%)
Visual hallucinations	10 (12%)	10 (12%)
Delusional	27 (33%)	27 (33%)
Cholinesterase inhibitor	2 (2%)	3 (4%)
Atypical neuroleptic before randomisation	57 (69%)	58 (71%)
SMMSE >6 points	11 (6 [n=83]); 16 (19%)	11 (5 [n=82]); 14 (17%)
SIB	71·1 (22·7 [n=75]); 77 (58–91)	73·8 (20·7 [n=71]); 80 (63–92)
NPI	17·4 (14·6 [n=75]); 15 (5–24)	15·8 (11·3 [n=70]); 14 (6–24)
FAST	5·7 (0·8 [n=72]); 6 (6–6)	5·5 (0·8 [n=72]); 6 (5–6)
mUPDRS ≥8 points	2·7 (3·8 [n=64]); 6 (9·4)	2·7 (3·9 [n=64]); 10 (15·6)
BADL	18·5 (9·0 [n=73]); 19 (12–24)	17·9 (9·5 [n=71]); 16 (12–23)
STALD (receptive)	3·8 (1·9 [n=59]); 4 (3–5)	4·4 (2·2 [n=58]); 5 (5–6)
STALD (expressive)	6·3 (3·0 [n=59]); 7 (4–9)	7·2 (2·8 [n=58]); 8 (5–10)
FAS	8·4 (7·3 [n=48]); 7 (3–13)	10·9 (7·9 [n=45]); 10 (5–14)

Data are number (%); mean (SD), range; median (IQR). EPS=extrapyramidal symptoms. SMMSE=standardised mini-mental state examination. SIB=severe impairment battery. NPI=neuropsychiatric inventory. FAST=functional assessment staging. mUPDRS=modified unified Parkinson's disease rating scale. BADL=Bristol activities of daily living scale. STALD=Sheffield test for acquired language disorders. FAS=functional assessment scale.

Table 1: **Demographic and clinical characteristics and assessments at baseline**

Statistical analysis

Demographic factors and clinical characteristics were summarised with counts (percentages) for categorical variables, mean (SD) for normally distributed continuous variables, or median (interquartile or entire range) for other continuous variables. Final mortality data were collected as of Sept 15, 2006, and a survival analysis was done on these data to produce Kaplan–Meier estimates with log rank tests. Hazard ratios (HR) and 95% CIs were estimated from the Cox regression model.

The principal analysis included everyone who received at least one dose of treatment (defined as modified intention-to-treat population [mITT]), in keeping with the main trial. To assess whether the section of the analysis population might have influenced the findings, additional analyses were done on all participants who were randomised (ITT population), which included those participants who never started their allocated treatment and those participants who received at least one dose of treatment, but excluded those who stopped the allocated treatment before 12 months. Cause of death (classified as probable vascular event, possible vascular event, or unrelated to vascular causes) was analysed with Fisher's exact test. SPSS (release 12.0.1) was used to enter and manage data, and Stata (release 9.2) was used for analyses.

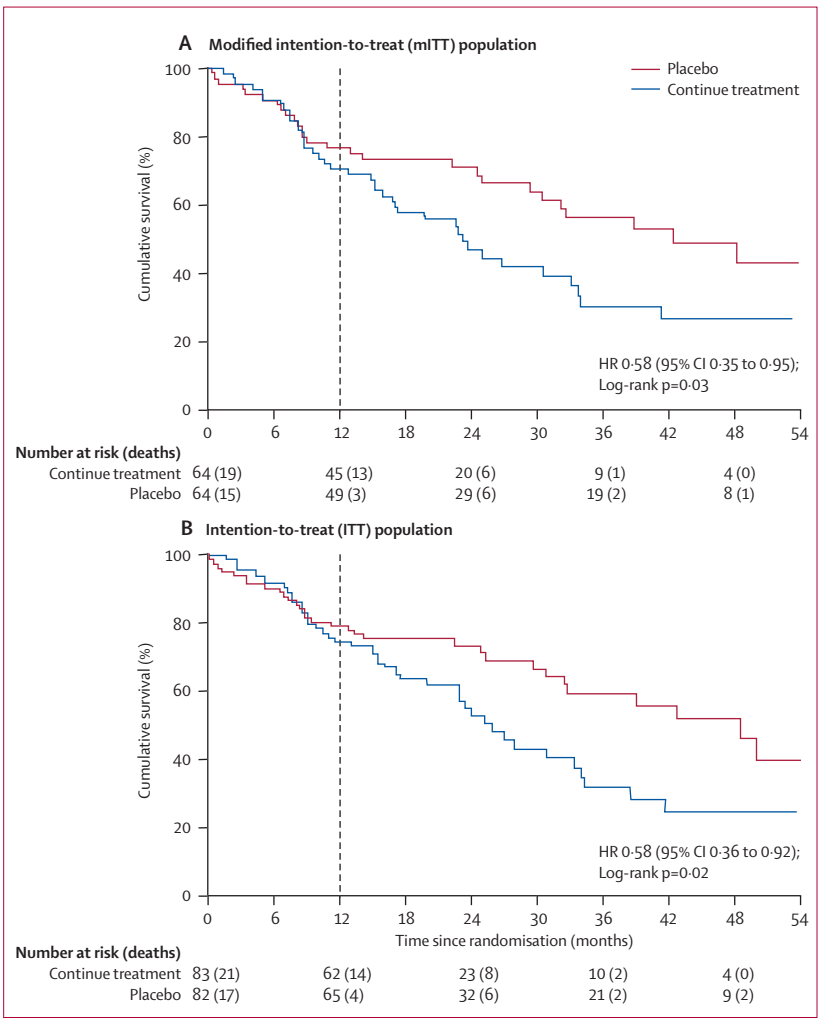

Figure 2: **Kaplan–Meier survival estimates**
The broken vertical line indicates the end of the 12-month randomised trial.

This trial is registered with the Cochrane Central Registry of Controlled Trials/National Research Register (ISRCTN33368770).

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. E Juszczak and L-M Yu had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

165 patients were randomised (83 to continue treatment and 82 to placebo [discontinue treatment]). Ten patients (12%) of those randomised to continue treatment and 16 patients (20%) of those randomised to placebo were prescribed high-dose treatment and all other patients were prescribed low-dose treatment. Although the protocol permitted participants to receive very low doses, no participants received this prescription. The most common treatments before randomisation were risperidone (52 in continue treatment, 49 in placebo) and haloperidol (23 in continue treatment, 20 in placebo), which accounted for 93% of prescriptions. 128 (78%) of the participants who were randomised started treatment (64 in the continued treatment group and 64 in the placebo group). Figure 1 shows the trial profile, and a full CONSORT chart of the first 12 months of the study is shown in the original publication of the cognitive and behavioral outcomes of the DART study.[10] The main reasons for not stopping open-label treatment and starting blinded treatment were withdrawal of consent by the participant, family, or family practitioner (n=27), or significant physical comorbidity or deterioration, including death or hospitalisation (n=5). Survival information was available for all the participants who were randomised. Baseline demographic and clinical characteristics were broadly similar across the two groups (table 1). Seven participants died and six participants withdrew from each treatment arm before the assessment at month 12. In the group allocated to continue antipsychotic treatment, the mean length of prescription in survivors was 25·1 months (95% CI 15·7–53·3 months). Of the patients assigned to placebo, only seven were subsequently restarted on antipsychotics, and they remained on placebo for a minimum of 12 months.

Comparisons between the patients who continued antipsychotic treatment and the placebo group during the 12-month randomised, double-blind phase of the trial showed that the respective cumulative probabilities of survival were 89·7% (95% CI 71·3%–96·5%) versus 97·1% (80·9–99·6%) in the patients who continued to take their allocated treatment for 12 months, 70·3% (57·5–79·9%) versus 76·6% (64·2%–85·2%) in the patients who started their allocated treatment (mITT population), and 74·7% (63·9–82·7%) versus 79·3% (68·8–86·6%) in the ITT population.

The Kaplan–Meier estimates (figures 2 and 3) show that during the extended follow up, the patients who continued antipsychotic treatment had significantly higher mortality compared with those who took placebo (mITT population log rank p=0·03, HR 0·58 [95% CI 0·35 to 0·95]; ITT population log rank p=0·02, HR 0·58 [0·36 to 0·92]). The difference in mortality was more pronounced after the first year. The differences in survival were similar whether the analysis was done on the mITT population, the ITT population, or on the patients who continued to take their allocated treatment for the first 12 months of the study (or until death, whichever occurred first). The only difference between the analyses was a clearer separation of the groups over the 12-month randomised period of the trial. On the basis of the results for the mITT population, the cumulative survival was 46% versus 71%, respectively, between the continued treatment and placebo groups at 24 months, 30% versus 59% at 36 months, and 26% versus 53% at 42 months. The

numerical differences at months 24, 36, and 42 were similar in the analyses for the ITT population and the patients who took their medication for the first 12 months.

Death certificates were obtained for 59 of 76 patients (78%) patients who died. More deaths due to probable vascular causes occurred in the placebo group (not significant), and there was no evidence of an increase in cerebrovascular deaths in the patients assigned to continue antipsychotics (tables 2 and 3). A limitation of such an analysis is that time to death is not accounted for. However, a strength is that the classification of whether mortality was probably or possibly related or was unrelated to a vascular event was done in blinded fashion, and the small number of disagreements were resolved by consensus.

Discussion

We report mortality in a long-term follow up of a cohort of patients with AD who participated in a randomised, placebo-controlled, antipsychotic withdrawal trial. During the 12 months of the randomised phase of the trial, there was an increase in mortality in the patients who continued antipsychotic treatment (5–8% greater than placebo, depending on the population analysed). Throughout the 54 months of follow up, there was a higher rate of mortality in the patients who were randomised to continue antipsychotic medication compared with those who were randomised to discontinue antipsychotic medication, particularly at 24, 36, and 48 months. The survival rates were similar in additional analyses that focused on the patients who continued their allocated treatment for at least 12 months. These results suggest a persistent risk of increased mortality with the long-term use of antipsychotics in patients with AD.

The reasons why the biggest differences in mortality occurred after the 12-month randomised phase of the trial are unclear, although the overall OR of risk during the first 12 months was similar to that reported in case register studies and to the extrapolated additional mortality reported in a meta-analysis of 12-week studies.[13,20,21] In addition, the analysis of patients who continued their allocated treatment for at least 12 months or until death showed a more clear separation of the survival plots between 6 months and 12 months of follow-up. One possible explanation for our findings is that the most frail participants who had the most severe dementia (ie, those most likely to die within 12 months) have a high mortality risk regardless of whichever treatment is assigned. Another possible explanation is that the close monitoring afforded during a clinical trial was able to mitigate the effect of important adverse outcomes. However, we must acknowledge that fewer participants were analysed at the later time points, at which the differences in survival were greatest; therefore, these results should be interpreted with caution.

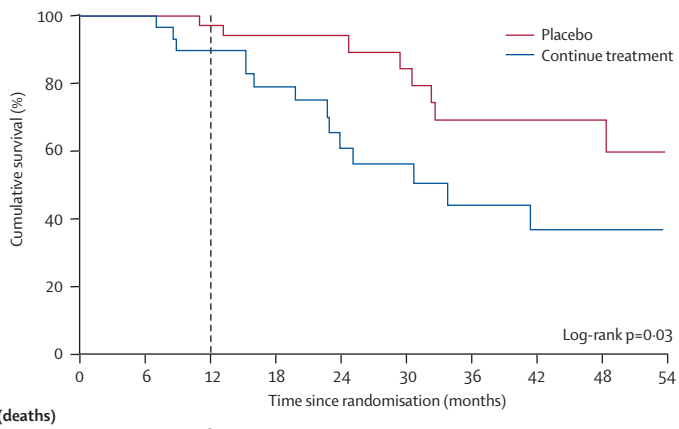

Figure 3: **Kaplan–Meier survival estimates of participants who received at least one dose of treatment and continued allocated treatment for 12 months**
The broken vertical line indicates the end of the 12-month randomised trial.

	Continue treatment (n=39)	Placebo (n=27)	Fisher's exact test p-value
No	16 (41%)	12 (44%)	0·06
Possible	9 (23%)	3 (11%)	0·06
Probable	2 (5%)	7 (26%)	0·06
Missing	12 (31%)	5 (19%)	..

Data are number (%).

Table 2: **Vascular causes of death by treatment in the mITT population**

	Continue treatment (n=45)	Placebo (n=31)	Fisher's exact test p-value
No	20 (44%)	15 (48%)	0·30
Possible	9 (20%)	4 (13%)	0·30
Probable	4 (9%)	7 (23%)	
Missing	12 (27%)	5 (16%)	

Data are number (%).

Table 3: **Vascular causes of death by treatment in the ITT population**

Most patients were prescribed risperidone (67%) or haloperidol (26%) before randomisation, and the results cannot necessarily be generalised to other atypical antipsychotics. Nevertheless, the results are consistent in that the patients allocated to discontinue antipsychotics seem to benefit from lower mortality during long-term follow up than those allocated to placebo. This work further emphasises the clinical imperative to review antipsychotic medication that is regularly prescribed, and to avoid protracted periods of treatment with antipsychotic drugs in people with dementia; the findings also reinforce the urgency to establish safe and effective pharmacological and non-pharmacological alternatives to antipsychotics.

We were able to assign most of the causes of death from studying the death certificates, particularly those

patients who died from cerebrovascular causes. In the current data, there was no evidence of excessively increased mortality due to cerebrovascular causes in the patients assigned to antipsychotic treatment. However, the modest numbers and the questionable accuracy of death certificate information should be noted because they preclude a definitive evaluation of specific causes of death in this study. Additionally, the sample size was too small and the data too limited to undertake an evaluation of the effect of cardiovascular and cerebrovascular risk factors on cause of death.

A difficulty in interpreting the data is the uncertainty about changes in prescribed medication in the patients who withdrew from the study, and about what happened after the 12-month placebo-controlled phase to those who completed. In particular, whether the patients allocated to the placebo group were prescribed an antipsychotic after the 12-month period or whether people allocated to an antipsychotic were withdrawn from treatment are unknown. From the final follow-up data, the mean duration of antipsychotic treatment was longer than 25 months over the course of the follow-up in the patients allocated to continue antipsychotic treatment. Also, only seven people from the initial placebo group who were assessed at the final follow up were restarted on an antipsychotic, and all of them took placebo for the 12-month randomised phase of the trial. Therefore, the group allocated to continue antipsychotic treatment in the double-blind phase of the trial had more exposure to antipsychotics throughout the whole study. Additionally, analysis of the patients who continued with their allocated treatment for at least 12 months showed a survival pattern similar to that of the overall trial population. On the basis of the available information, a significant effect of changes in treatment on the results of the survival analysis seems unlikely.

Another potential limitation in the generalisability of the results is that participants were only included if they had an MMSE score higher than 6 points or a SIB score higher than 30 points. These inclusion criteria were in place because one of the objectives of the original placebo-controlled phase of the DART trial was to assess the effect of antipsychotic treatment on cognition; therefore, the avoidance of floor effects was deemed important. One consequence, however, is that the patients with most impairment, who are likely to be at the highest risk of mortality, were excluded from the trial.

The authors of the recent Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study,[8] a large, pragmatic, 36-week, placebo-controlled trial of atypical antipsychotics in AD, concluded that the modest benefits were not sufficient to justify therapy owing to the increased risk of serious adverse events. Our data add further serious safety concerns about the long-term use of antipsychotics in this population, and clinicians should certainly try to replace antipsychotics with safer management approaches. Several studies have shown that psychological management can replace antipsychotic therapy without any appreciable worsening of neuropsychiatric symptoms;[17,25] and although cholinesterase inhibitors do not seem to be an effective short-term pharmacological treatment for agitation,[26] there is evidence that memantine[27] or antidepressants such as citalopram[28] might be safer and effective alternatives for some neuropsychiatric symptoms.

Our opinion is that there is still an important but limited place for atypical antipsychotics in the treatment of severe neuropsychiatric manifestations of AD, particularly aggression. However, the accumulating safety concerns, including the substantial increase in long-term mortality, emphasise the urgent need to put an end to unnecessary and prolonged prescribing.

Contributors

CB, MLH, RMcS, RJ, and EJ participated in the original design of the study, study governance, supervising study recruitment, and preparing the first and subsequent drafts of the manuscript. MT, SD, and KK participated in study recruitment, data collection and entry, and preparing the first and subsequent drafts of the manuscript. RG participated in data collection and entry, and the preparation of the first and subsequent drafts of the manuscript. L-MY participated in monitoring of data quality, data analysis, and preparing the first and subsequent drafts of the manuscript.

Conflicts of interest

Within the past 5 years, CB has received honoraria from Novartis, Pfizer, Shire, Lundbeck, Myriad, Servier, and Arcadia, and research grants from Novartis and Lundbeck; and honoraria and research grants from AstraZeneca and Janssen more than 5 years ago. None of the other authors has any conflicts of interest.

Acknowledgments

This study was supported by a grant from the UK Alzheimer's Research Trust to CB, RJ, and RMcS.

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