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Metabolic syndrome and drug discontinuation in schizophrenia: a randomized trial comparing aripiprazole olanzapine and haloperidol

Parabiaghi A, Tettamanti M, D'Avanzo B, Barbato A. Metabolic syndrome and drug discontinuation in schizophrenia: a randomized trial comparing aripiprazole olanzapine and haloperidol

Objective: To determine whether the prescription of aripiprazole, compared with olanzapine and haloperidol, was associated with a lower frequency of metabolic syndrome (MS) and treatment discontinuation at 1 year.
Method: Patients were randomly assigned to be treated open-label and according to usual clinical practice with either aripiprazole, olanzapine, or haloperidol and followed up for 1 year.
Results: Three hundred out-patients with persistent schizophrenia were recruited in 35 mental health services. The intention-to-treat (ITT) analysis found no significant differences in the rate of MS between aripiprazole (37%), olanzapine (47%), and haloperidol (42%). Treatment discontinuation for any cause was higher for aripiprazole (52%) than for olanzapine (33%; OR, 0.41; $P = 0.004$), or haloperidol (37%; OR, 0.51; $P = 0.030$). No significant difference was found between olanzapine and haloperidol. Time to discontinuation for any cause was longer for olanzapine than for aripiprazole (HR, 0.55; $P < 0.001$). No significant differences were found between haloperidol and aripiprazole, or between olanzapine and haloperidol.
Conclusion: The prescription of aripiprazole did not significantly reduce the rates of MS, but its treatment retention was worse. Aripiprazole cannot be considered the safest and most effective drug for maintenance treatment of schizophrenia in routine care, although it may have a place in antipsychotic therapy.

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Key words: antipsychotic drugs; adverse effects; clinical trial; effectiveness

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†The details of GiSAS Study Group Information is given in Appendix 1.

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Significant outcomes

- The largest differences in the rates of metabolic syndrome (MS) at 1 year were found between aripiprazole and olanzapine, ranging from 9.6% in all randomized patients to 13.6% in treatment completers, and were always below the level of statistical significance.
- Retention on treatment with aripiprazole was significantly worse than with olanzapine and haloperidol, and this was attributed to reduced effectiveness.

Limitations

- The results cannot be applied to drug-naive patients or to patients with a brief history of illness.
- The sample size was reduced to 40% of that originally planned, and although it remained relatively large, it could have been insufficient to detect as statistically significant a difference around 10% in the 1-year rates of MS between aripiprazole and olanzapine.
- Incomplete follow-up data meant we could not formulate a per-protocol diagnosis of MS for 24% of the sample.
- Clinicians' knowledge of treatment could have influenced the assessment of weight and blood pressure and therefore, to some extent, the identification of metabolic syndrome.

Introduction

Antipsychotics (APs) are a mainstay of treatment for schizophrenia (1), although recent evidence casted doubt on their effects on long-term recovery (2). First-generation antipsychotics (FGAs) offer short-term benefits in controlling positive symptoms, although with high rates of extrapyramidal side-effects (3, 4). Second-generation antipsychotics (SGAs) have not yet shown clear advantages, as they can cause weight gain and alter lipid and glucose metabolism (5, 6). Differences in efficacy between APs are small, by contrast with robust differences in side-effects (7, 8). These drugs should be considered a mix of compounds with nothing that clearly distinguishes the different classes (8).

Most trials of APs were explanatory trials conducted for registration purposes and focused on efficacy not effectiveness. Recruitment of highly selected samples (9) made comparisons uneven and limited the external validity of the results. Five major large, pragmatic and independent trials have investigated the effectiveness of FGAs and SGAs in schizophrenia (10–14). A recent review concluded that effectiveness research in this field is still inconclusive (15). However, these trials have contributed to changes in treatment recommendations. SGAs are no longer the undisputed first-line treatment and the question revolves around the side-effect risks of FGAs and specific SGAs (16, 17).

Unresolved issues in AP treatment are confirmed by high rates of discontinuation in naturalistic studies (18, 19) and by concerns that the iatrogenic effects of APs could be among the risk factors for the excess mortality in schizophrenia (20). Attention focused on metabolic syndrome (MS) as a risk marker for cardiovascular disorders (21). Not surprisingly, high prevalence rates of MS have been found in people with a long exposure to AP treatment (22).

Aripiprazole, first licensed in Europe in 2004, raised interest for its pharmacological profile, and, in fact, preliminary opinions on its efficacy and tolerability were optimistic (23). Some reports showed low rates of MS in long-term patients with schizophrenia (24), and comparisons of metabolic side-effects of SGAs showed that aripiprazole induced less weight gain and less increase in glucose and cholesterol than olanzapine (25). However, the findings were based on two studies only.

Aripiprazole has never been included in any major pragmatic trial on schizophrenia (15) and information on comparisons with other APs has been considered of limited quality (26, 27). A recent meta-analysis concluded that data on aripiprazole are sparse, and there is a need for large, independent pragmatic trials to assess its effectiveness (26).

The Italian Study Group of Second-Generation APs (GiSAS) designed, in 2007, a trial to evaluate the safety and effectiveness of aripiprazole, olanzapine, and haloperidol in an unselected sample of people with schizophrenia over 1 year. The goal was to compare the effects of the recently introduced aripiprazole with two well-known drugs with different pharmacological profiles: haloperidol and olanzapine.

Aims of the study

The GiSAS trial aimed to produce clinically relevant information. It was large enough to identify moderate differences in treatment effects and simple enough to be implemented in everyday clinical practice with minimal additional work. It focused on tolerability and effectiveness: the primary endpoint was MS, and the secondary endpoint was treatment discontinuation. The study hypothesis is that aripiprazole offers a lower frequency of MS and better drug retention than olanzapine and haloperidol.

Material and methods

Study design

This was an independently funded, pragmatic, parallel group, open-label, data-analyst-blinded randomized controlled trial rooted in everyday clinical practice. The study rationale and protocol have been described in detail (28). To enhance representativeness, the inclusion criteria were wide, with recruitment in a broad array of settings.

The protocol was approved by the review boards of all participating centers and made available to all study investigators. As explained elsewhere, the protocol was amended to reduce the planned sample size of 250 patients per arm and to prolong recruitment (28). The trial is registered in the EU Clinical Trials Register (EudraCT number 2007-000278-22) and in ClinicalTrials.gov (NCT01052389). The protocol can be obtained from the corresponding author.

Participants

The study was planned and coordinated by a research group based at IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy. Forty-three centers (7 medical schools and 36 national health service (NHS) trusts) in 14 of the 20 Italian regions participated in the study, and patients were enrolled from October 2007 to June 2011. Clinicians were asked to screen for eligibility all patients over 18 years with a DSM IV diagnosis of schizophrenia based on the Mini-International Neuropsychiatric Interview (29) who could benefit from changing treatment with an oral AP. The last inclusion criterion represented the key starting point of the trial. Given the possibility of changing treatment, patients should have been randomized only if the current medication was somehow unsatisfactory or if there was evidence of clinical unmet needs. This criterion was operationalized and thoroughly described in the study manual and recruitment form. The presence of MS was assessed by clinicians on the basis of the criteria indicated by the Adult Treatment Panel III (ATP III) (30): abdominal obesity (waist circumference >102 cm in men or >88 cm in women); fasting triglycerides ≥150 mg/dl; high-density lipoprotein <40 mg/dl in men or <50 mg/dl in women; hypertension (≥130/85 mmHg or on antihypertensive medication); hyperglycemia (fasting glucose ≥110 mg/dl or on insulin or hypoglycemic medication). Exclusion criteria were as follows: MS (at least three of the five ATP III criteria) (25), diabetes mellitus type II, specific contraindications to one of the study drugs (including evidence from patient's medical history of the ineffectiveness or harm of one of the drugs), and no previous exposure to APs.

Patients were recruited in any psychiatric setting: community mental health centers, general hospital in-patient units, residential facilities, and day centers. Patients considered for inclusion were asked to provide informed consent, then enrolled. Eight centers did not refer any patient, so patients were recruited from 35 centers.

The sample was heterogeneous and reflected the real population attending psychiatric services. The study did not replace any aspect of the usual clinical care. Patients were seen as clinically indicated. All assessments and examinations were carried out locally by the treating teams.

Procedures

Eligible patients were randomized 1 : 1 : 1 to non-blind oral monotherapy with one of the study drugs: aripiprazole, olanzapine, and haloperidol. The computer-generated allocation sequence was site-stratified in fixed blocks (first block was of nine, followed by blocks of three) and was registered before trial start. Investigators were unaware of the randomization scheme. Concealment was achieved by central randomization by telephone registration with an interactive voice response system. All records (failed calls, consecutive, or unregistered randomizations) were monthly examined to detect attempts to decipher allocation.

All people involved in trial coordination, primary outcome assessment, and data analysis were blinded. Masking was maintained by omitting in case report forms any clue that could reveal the study drug and using a masked code for treatment groups in all analyses. Study investigators and monitors were specifically instructed to never mention the name of the study drug. Blood tests to detect metabolic disturbances at follow-up were performed in an independent reference laboratory. All data were examined after the study database was locked. Analyses were performed at Mario Negri Institute by a separate unit whose personnel was not involved in the study conduction. The randomization code was broken at study completion, after the primary analysis.

After randomization, the study drugs were prescribed and dispensed according to usual practice and individual response. The clinicians were free to treat patients at their own discretion; no specific strategies to maintain or improve compliance were recommended. Concomitant medication was

allowed. After tapering previous medication, the use of concomitant APs was considered treatment failure.

Patients were assessed at baseline, at discontinuation of monotherapy, and at 1 year. Centralized blood tests were carried out at baseline to check the accuracy of clinicians' MS diagnoses. Patients positive for MS were not excluded from the primary ITT analysis but were excluded from the per-protocol (PP) analysis.

Clinicians were unobtrusively prompted to monitor adherence and reasons for discontinuation were collected. General clinical data and information on psychosocial interventions, hospital or residential admissions were drawn from patient records. The study followed European standard good clinical practice guidelines and its phases were recorded following the CONSORT statement for reporting pragmatic trials (31). All patients were treated as out-patients by the reference mental health service.

Outcome measures

The proportion of patients positive for MS at 1 year was the primary endpoint. For the ATP III diagnosis of MS at follow-up, centralized blood tests results were utilized.

The 1-year discontinuation of the allocated therapy, defined as switching to another AP, adding a second AP or stopping the assigned drug, was the main secondary endpoint. All-cause discontinuation was considered treatment failure (except stopping the drug for clinical remission). Discontinuers were still followed for the rest of the study. Time to discontinuation and reasons for discontinuing were also analyzed.

Statistical analysis

For the primary outcome, the following populations were analyzed: (i) ITT population (the primary analysis population: all randomized patients), (ii) PP population (patients who were confirmed free from MS at baseline by centralized analysis and took at least 30 days of the allocated treatment), (iii) complete case (CC) population (patients who had full MS information at follow-up), and (iv) compliant and complete case (CCC) population (patients who had full information on MS parameters and were still on the allocated monotherapy at follow-up).

The first step of the primary analysis was logistic regression with treatment as independent variable and centers as a random effect. In the second step, pairwise analyses were performed using Hochberg adjustment. Odds ratios with confidence intervals were calculated for each population.

Guidelines on how to handle missing outcome data in randomized controlled trials recommend to perform multiple analyses using different approaches and under different assumptions (32). Thus, to correct for missing MS diagnoses at 1 year, we imputed the value in two different ways, using simple imputation [last observation carried forward (LOCF) for patients with the presence/absence of MS at treatment discontinuation and worst outcome (WO) for the others] or multiple imputation (MI). Two MI approaches were used: (i) MI for all patients without MS diagnosis at 1 year and (ii) inference of MS from information on blood pressure and waist-to-height ratio (33) (WHtR) or MI for the others. We decided to use WHtR instead of waist circumference because it is considered a better screening tool for adult cardiovascular risk factors (33) and because, in our sample, it correlated with MS better than the other anthropometric parameters. Baseline variables chosen as MI regressors were as follows: age, sex, systolic and diastolic blood pressure, GAF score, waist circumference, height, physical activity, alcohol consumption, and smoking status.

To further explore the differences among groups, two other secondary MI analyses were performed: MI direct imputation of outcome and MI imputation starting with age and sex only. As no multivariate normality could be assumed, a bootstrap method was used. Analyses with replacement of missing data were performed on ITT and PP populations.

The secondary analysis comparing differences in the proportion of patients who discontinued treatment at 1 year and in time to discontinuation was performed only on the ITT population. For the analysis on proportions, the primary analysis method was repeated. Differences in time to discontinuation between aripiprazole and olanzapine, or between aripiprazole and haloperidol were evaluated using Hochberg-adjusted log-rank tests and Cox proportional hazards models.

Centers with fewer than nine patients were grouped on a geographical basis. Data checking and handling were done with JMP PRO v 10.0 (SAS Institute Inc., Cary, NC, USA). Analyses were performed with STATA v 12.1 (StataCorp, College Station, TX, USA).

Sample size and power

In the first version of the study protocol, three Hochberg-adjusted comparisons were planned. On the basis of available evidence (34–37), it was

hypothesized that the percentage of patients who would develop MS was 25% in the olanzapine group, 15% in the haloperidol group, and 5% in the aripiprazole group. Thus, 250 subjects per group were calculated to correspond to a power of 80% (olanzapine vs. haloperidol), 93% (haloperidol vs. aripiprazole), and more than 99% (olanzapine vs. aripiprazole). As is common in trials, inclusion of enough patients in the GiSAS study has been a problem. Thus, we had to reduce the sample to 40% of the original size. To preserve the study power, we cut one of the planned comparisons and focused on aripiprazole vs. olanzapine, and aripiprazole vs. haloperidol. After protocol revision (28), the risk of developing MS was estimated as 25% in the olanzapine group, 20% in the haloperidol group, and 5% in the aripiprazole group. The study hypothesis was changed only for haloperidol. This choice was supported by incoming evidence showing similar rates of emerging MS for haloperidol and olanzapine (38). Thus, we calculated that a sample of 80 patients per arm would gave 77% power to detect a minimal important difference of 15% between aripiprazole and haloperidol (at $P = 0.05$), and 87% power to detect a clinically significant difference of 20% between aripiprazole and olanzapine (at $P = 0.025$). The comparison of olanzapine and haloperidol was considered as secondary. A sample size of 240 subjects had 89% power to yield a statistically significant result. Assuming a drop-out rate of 10%, 264 patients were required.

Results

Patient flow and characteristics

Figure 1 shows the patients' progress through the trial. A total of 1261 patients were assessed for eligibility, but 961 (76%) could not be included, most of them because they did not need to change current treatment (476; 71%). Overall, 300 subjects were randomized by 76 investigators, 100 to aripiprazole, 103 to olanzapine, and 97 to haloperidol. No significant differences in baseline characteristics were found between the randomized patients and those excluded for various reasons.

The main characteristics of the three groups are shown in Table 1. Before randomization, 41 patients (14%) were taking depot FGAs and 8 (3%) depot SGAs. Eighty-two (33%) patients were taking oral FGAs and 195 (79%) oral SGAs. Forty-six patients (16%) were receiving more than one AP; 17 (18%) of these were randomized to aripiprazole, 13 (13%) to olanzapine, and 16 (17%) to haloperidol. Sixty-eight patients (23%) were randomized to continue the same AP.

The treating clinicians of 207 (69%) patients rated adherence to previous AP regimens satisfactory, 194 (64%) patients had positive attitudes toward AP efficacy, and 180 (60%) rated as positive previous experience with side-effects.

Only four patients did not receive the allocated medication, two in the aripiprazole group, one in the olanzapine group, and one in the haloperidol group.

Rates of additional medications prescribed to patients were low, ranging, on all subjects, from 13.3% for benzodiazepines to 3% for antiparkinson drugs. The only significant difference among groups was found in antiparkinson drugs, prescribed to 6.2% of patients in the haloperidol group by contrast with none in the aripiprazole group ($P = 0.03$).

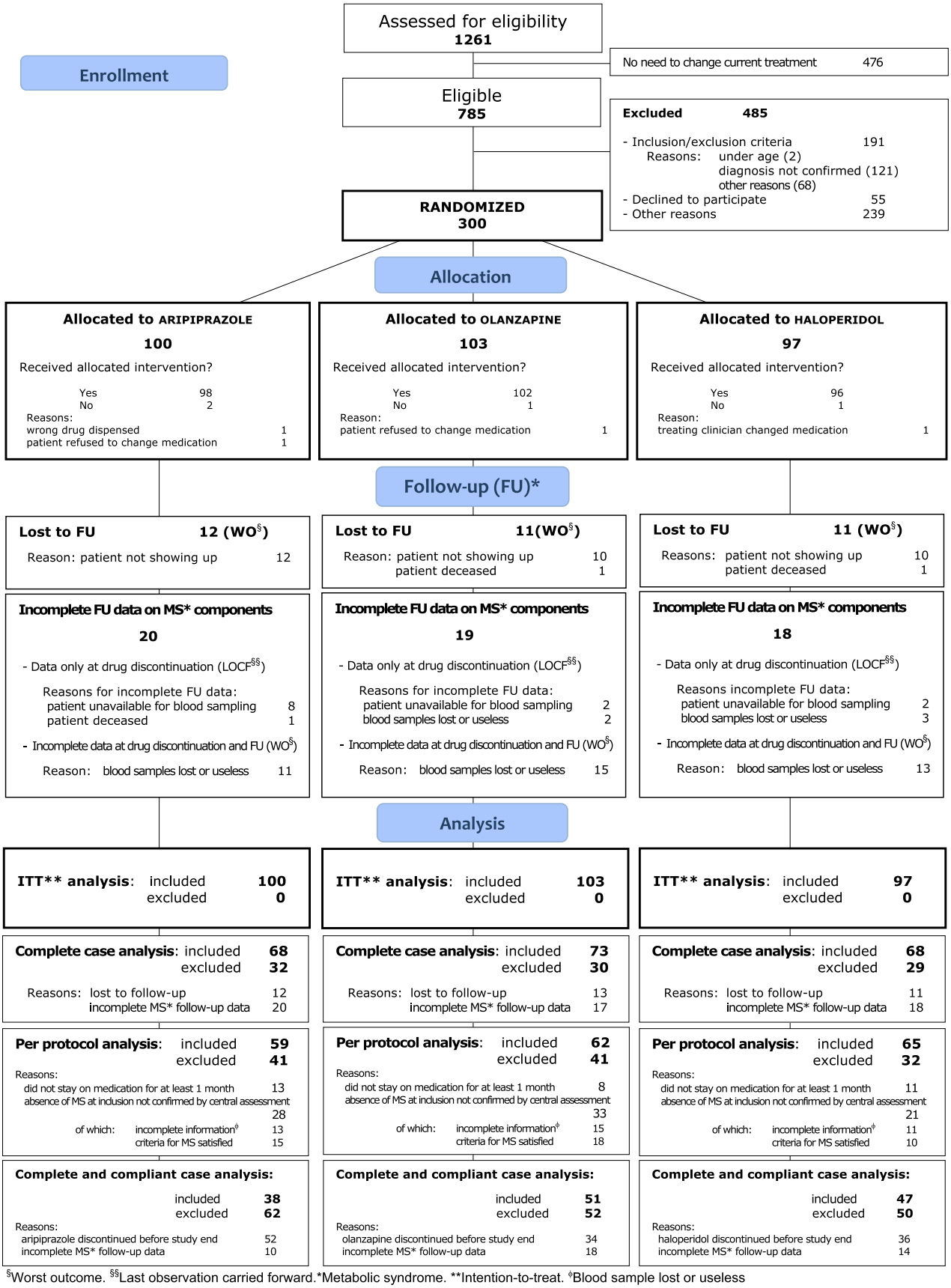
Treatment effect on metabolic syndrome

Table 2 shows the primary ITT analysis of the difference in the proportions of patients positive for MS at 1 year, including results from MI of missing data, and the secondary analyses of this outcome on the other populations. No significant differences were found among treatment groups in the primary and secondary comparisons.

Looking at differences in the five criteria of MS, the only significant difference at follow-up was found in rates of hyperglycemia (aripiprazole 14%, haloperidol 7%, olanzapine 1%; $P = 0.01$). The estimates for different treatments appeared unchanged after inserting baseline lipid values as covariates in the model containing treatments and centers. As well, they showed no effect interaction.

Treatment effect on drug discontinuation

Table 3 and Figure 2 show treatment effect on secondary outcome of effectiveness. A higher proportion of patients discontinued treatment for any cause with aripiprazole (52%) than with olanzapine (33%; odds ratio, 0.41; $P = 0.004$) or haloperidol (37%; odds ratio, 0.51; $P = 0.030$). No significant difference was found between the olanzapine and haloperidol groups. 94% of subjects who discontinued were switched to other APs, 6% stopped taking the assigned drug and did not accept any further AP treatment. In the aripiprazole group, 45% of switched patients were prescribed haloperidol, 24% olanzapine,18% risperidone, and 13% clozapine. In the olanzapine group, 45% were prescribed haloperidol and 21% risperidone. In the haloperidol group, 27% were



§Worst outcome. §§Last observation carried forward.*Metabolic syndrome. **Intention-to-treat. ♦Blood sample lost or useless

Fig. 1. Study flow chart.

Table 1. Baseline sociodemographic and clinical characteristics of randomized patients by treatment arm

	ARI (n = 100)	OLA (n = 103)	HAL (n = 97)	All subjects (n = 300)
Sociodemographic characteristics				
Sex, n (%)				
M	55 (55)	66 (64)	54 (56)	175 (58)
Age, mean (SD)	40.2 (12.4)	44.1 (12.8)	43.9 (12.2)	42.7 (12.5)
Place of living, n (%)				
At home	88 (88)	92 (89)	83 (86)	263 (88)
Residential facility	7 (7)	8 (8)	11 (11)	26 (9)
Other	2 (2)	2 (2)	1 (1)	5 (2)
Living arrangement, n (%)				
Alone	77 (77)	76 (74)	74 (76)	227 (76)
With relatives	9 (9)	9 (9)	16 (17)	34 (11)
With others	4 (4)	3 (3)	2 (2)	9 (3)
Psychiatric history				
Years from first psychiatric contact, n (%)				
0-2 years	12 (12)	12 (12)	13 (13)	37 (12)
3+ years	68 (68)	78 (76)	69 (71)	215 (72)
Patient status at baseline, n (%)				
In-patient	20 (20)	15 (15)	25 (26)	60 (20)
Out-patient	76 (76)	87 (85)	69 (71)	232 (77)
Current substance abuse or dependence, n (%)				
Yes	9 (9)	2 (2)	4 (4)	15 (5)
No	86 (86)	100 (97)	92 (95)	278 (93)
Lifetime suicide attempts, n (%)				
Yes	21 (21)	13 (13)	10 (10)	44 (15)
No	76 (76)	87 (84)	86 (89)	249 (83)
Baseline clinical characteristics				
Weight (Kg)				
Mean (SD)	73.2 (14.3)	76.8 (16.0)	76.0 (14.5)	75.4 (15.0)
Waist circumference, cm				
Mean (SD)	92.7 (15.2)	96.6 (14.4)	95.3 (15.3)	94.9 (15.0)
Waist-to-height ratio (WHtR)				
Mean (SD)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)
Diastolic blood pressure				
Mean (SD)	78.1 (7.6)	78.9 (7.8)	79.1 (7.3)	78.7 (7.6)
Systolic blood pressure				
Mean (SD)	123.4 (13.5)	122.0 (11.6)	123.5 (11.1)	123.0 (12.1)
Fasting triglycerides				
Mean (SD)	135.4 (66.2)	131.6 (68.9)	135.4 (66.2)	139.0 (78.7)
High-density lipoprotein (HDL)				
Mean (SD)	43.3 (12.6)	43.4 (11.3)	44.9 (14.2)	43.9 (12.7)
Fasting glucose				
Mean (SD)	92.8 (16.7)	87.9 (13.0)	87.6 (18.0)	89.4 (16.2)
Prolactin				
Mean (SD)	20.6 (24.4)	19.5 (18.9)	23.9 (25.7)	21.4 (23.2)
QTc				
Mean (SD)	398.6 (29.8)	395.6 (31.3)	397.6 (36.2)	397.2 (32.5)
BPRS total score				
Mean (SD)	58.1 (17.1)	57.1 (20.0)	57.9 (19.6)	57.7 (18.9)
GAF score				
Mean (SD)	47.5 (13.8)	48.6 (16.1)	50.2 (15.2)	48.8 (15.1)
LUNSERS score				
Mean (SD)	27.9 17.4	28.8 16.8	30.0 19.0	28.9 17.7
AP treatment before randomization				
Type of medication, n (%)				
Oral AP	80 (80)	76 (74)	69 (71)	225 (75)
Depot	4 (4)	15 (15)	7 (7)	26 (8)
Both	7 (7)	4 (4)	12 (12)	23 (8)
None	5 (5)	5 (5)	8 (8)	18 (6)
Oral APs, n (%)*				
Aripiprazole	11 (12.6)	7 (8.8)	6 (7.4)	24 (9.7)
Clozapine	5 (5.7)	4 (5.0)	5 (6.2)	14 (5.6)
Haloperidol	22 (25.3)	16 (20.0)	25 (30.9)	63 (25.4)
Olanzapine	30 (34.5)	32 (40.0)	16 (19.8)	78 (31.5)
Risperidone	16 (18.4)	15 (18.8)	18 (22.2)	49 (19.8)
Other FGAs†	4 (4.6)	8 (10.0)	7 (8.6)	19 (7.7)
Other SGAs‡	11 (12.6)	8 (10.0)	11 (13.6)	30 (12.1)

Percentages do not add up to 100% due to missing data.

AP, antipsychotic; ARI, aripiprazole; OLA, olanzapine; HAL, haloperidol.

*Some patients were taking more than 1 AP concurrently; percentages were calculated on the number of patients taking at least 1 oral AP: 87 in the aripiprazole group, 80 in the olanzapine group, and 81 in the haloperidol group.

†Levomepromazine; penfluridol; perphenazine; pimozide; promazine; zuclopenthixol; clotiapine; bromperidol; chlorpromazine.

‡Amisulpride; quetiapine; paliperidone.

prescribed aripiprazole, 23% quetiapine, and 19% olanzapine.

The time to discontinuation for any cause was longer in the olanzapine than in the aripiprazole group (hazard ratio, 0.55; $P < 0.001$). No significant differences were found between haloperidol and aripiprazole, or between olanzapine and haloperidol.

The rate of discontinuation for lack of efficacy was higher for aripiprazole than for olanzapine (odds ratio, 0.44; $P = 0.017$), and haloperidol (odds ratio, 0.48; $P = 0.032$). No significant difference was found between olanzapine and haloperidol.

The time to discontinuation for lack of efficacy was longer for olanzapine than for aripiprazole (hazard ratio, 0.46; $P = 0.001$). No significant differences were found between haloperidol and aripiprazole, or between olanzapine and haloperidol.

There were no significant differences between groups in the proportion of patients who discontinued treatment for side-effects or for their own decision. Only one patient, in the haloperidol group, discontinued treatment for clinical remission.

During the study, there were few adverse events with no differences between groups. One patient from each group died for reasons not attributable to trial participation. Twenty percentage of patients in the aripiprazole group, 12% in the olanzapine group, and 14% in the haloperidol group were admitted to psychiatric in-patient services; hyperprolactinemia was found in 12% of the aripiprazole group, 19% of the olanzapine group, and 22% of the haloperidol group.

Discussion

The prescription of aripiprazole was not associated with less frequent MS than olanzapine and halo-

Table 2. Primary ITT and secondary subpopulation analyses on the difference in the one-year proportion of patients positive for metabolic syndrome (MS)

	ARI	OLA	HAL	*P* value*
Direct imputation (DI) of missing values†				
ITT primary analysis				
Patients (*n*)	100	103	97	
MS at 1 year, *n* (%)	37 (37.0)	48 (46.6)	41 (42.3)	0.39
OR (95% CI)	1 (ref)	1.5 (0.8–2.6)	1.2 (0.7–2.2)	
PP secondary analysis				
Patients (*n*)	59	62	65	
MS at 1 year, *n* (%)	15 (25.4)	22 (35.5)	21 (32.3)	0.50
OR (95% CI)	1 (ref)	1.6 (0.7–3.5)	1.4 (0.6–3.1)	
Multiple imputation (MI) of missing values				
ITT secondary analyses				
Only MI				
Patients (*n*)	100	103	97	
MS at 1 year *n*‡ (%)	23 (23.2)	32 (30.7)	28 (28.4)	0.40
OR (95% CI)	1 (ref)	1.6 (0.8–3.3)	1.4 (0.6–3.0)	
DI of a surrogate diagnosis of MS§ and MI				
Patients (*n*)	100	103	97	
MS at 1 year, *n*‡ (%)	20 (20.0)	28 (27.7)	25 (25.6)	0.49
OR (95% CI)	1 (ref)	1.5 (0.7–3.3)	1.4 (0.6–3.0)	
No missing values				
CC secondary analysis				
Patients (*n*)	68	73	68	
MS at 1 year, *n* (%)	12 (17.6)	22 (30.1)	17 (25.0)	0.23
OR (95% CI)	1 (ref)	2.0 (0.9–4.5)	1.6 (0.7–3.6)	
CCC secondary analysis				
Patients (*n*)	38	51	47	
MS at 1 year, *n* (%)	6 (15.8)	15 (29.4)	10 (21.3)	0.31
OR (95% CI)	1 (ref)	2.2 (0.8–6.4)	1.4 (0.5–4.4)	

ARI, aripiprazole; OLA, olanzapine; HAL, haloperidol; WO, worst outcome; LOCF, last observation carried forward; ITT, intention to treat; PP, per protocol; CC, complete case; CCC, complete and compliant case; MI, multiple imputation; DI, direct imputation.

*Overall logistic regression.

†Direct imputation of LOCF and WO data.

‡Values were back-calculated from the estimated percentages.

§Diagnosis of MS from the following criteria: waist-to-height ratio (WHtR) ≥0.56 in men or ≥0.54 in women, and blood pressure ≥130/85 mmHg or on antihypertensive medication (following ATC classes: C02, C03, C07, and C08).

peridol. Moreover, retention on treatment with aripiprazole was worse, and clinicians ascribed this to lack of efficacy, which is consistent with evidence showing that lack of efficacy is the major cause of AP discontinuation (8).

First of all, we point out a limitation in the interpretation of the results. We enrolled patients with a long illness history and previous exposure to APs treatment. Therefore, our findings cannot be applied to drug-naive patients or to patients with a short illness history.

The reasons why the trial failed to find a clinical advantage for aripiprazole in terms of metabolic disturbances should be discussed. The difference between aripiprazole and olanzapine in the rates of MS at follow-up ranged from 9.6% in the primary ITT population to 13.6% in the CCC population and was always below the meaningful difference assumed (i.e., 20%). We acknowledge that the proposed *a priori* difference might have been too large. However, given the observed rate of MS in the olanzapine arm (47%), this difference would correspond to a number needed to treat of 5 (95% CI, 3.1, 15.1), which is a relevant, although restrictive, clinical aim (39).

The second possibility is that sample size and statistical power were too small. However, given the observed rate of MS in the olanzapine arm, the sample had an adequate 84% power to detect the hypothesized clinically significant difference of 20% from aripiprazole. On the other hand, the detection of a significant difference of 9.6% between aripiprazole and olanzapine in the ITT analysis would have required an unrealistically large sample of more than 400 patients per arm (β=0.8; α=0.05).

Third, we have to consider limits in the study design or implementation, particularly, the absence of blinding and missing follow-up data. The open nature of the study need not be considered a weakness. It enhanced its feasibility and reflected real clinical practice, increasing external validity and the generalizability of the results. What was randomized, after all, was the 'intention to openly treat' with these drugs, which is the intervention patients would have received in the real world, and this moved the trial toward the pragmatic side of the pragmatic-explanatory continuum (40). Nevertheless, we acknowledge that clinician awareness of the treatment could have influenced the assessment of weight and blood pressure and therefore the identification of MS. However, as blood tests were done blindly, any influence on the MS diagnosis should have been small. On the other hand, the influence of clinicians' or patients' expectations on drug retention could have been larger.

Missing data meant we could not formulate a proper diagnosis of MS for 24% of the sample. However, only half were actually lost to follow-up. For the others, part of the full set of MS components was available and this allowed us to formulate a surrogate diagnosis of MS. The main loss of blood samples was due to the earthquake of L'Aquila, where the study coordinating center for southern Italy was located. The involvement of real-world health services prevented us from using electronic medical records, and the decision to cause minimum extra work to clinical staff, adopting a non-intrusive approach, limited our ability to retrieve information. Missing data were distributed equally between arms, and it appeared that they were missing at random. All available options for dealing with missing data were explored, including a number of sufficiently powered sensitivity

Table 3. Outcome measures of effectiveness in the ITT population

	ARI (100)	OLA (103)	HAL (97)	*P* value
Treatment, mg/day				
Mean* (SD)	19.7 (8.7)	13.7 (5.6)	4.0 (2.8)	–
Median† (25th–75th percentile)	20.0 (11–30)	10.0 (10–20)	3.0 (2–6)	–
Discontinuation of treatment for any cause				
No. of patients (%)	52 (52.0)	34 (33.0)	36 (37.1)	**0.01**‡
OLA, odds ratio (95% CI)	**0.41 (0.23–0.76)**		0.81 (0.44–1.49)	–
HAL, odds ratio (95% CI)	**0.51 (0.28–0.94)**			
Kaplan–Meier time to discontinuation (days), 75th percentile (95% CI)	70 (40–99)	216 (99–365)	91 (44–244)	**0.02**
Cox-model treatment comparisons				
OLA, hazard ratio (95% CI)	**0.55 (0.42–0.73)**		0.82 (0.46–1.47)	–
HAL, hazard ratio (95% CI)	0.67 (0.42–1.07)			
Discontinuation of treatment for lack of efficacy§				
No. of patients (%)	32 (32.0)	18 (17.5)	18 (18.6)	**0.03**‡
OLA, odds ratio (95% CI)	**0.44 (0.23–0.86)**		0.92 (0.45–1.90)	–
HAL, odds ratio (95% CI)	**0.48 (0.25–0.94)**			
Cox-model treatment comparisons				
OLA, hazard ratio (95% CI)	**0.46 (0.29–0.74)**		0.92 (0.51–1.66)	–
HAL, hazard ratio (95% CI)	0.50 (0.24–1.03)			
Discontinuation of treatment for side-effects§				
No. of patients (%)	6 (12.6)	6 (18.8)	8 (22.2)	0.76‡
OLA, odds ratio (95% CI)	0.98 (0.30–3.19)		0.69 (0.23–2.10)	–
HAL, odds ratio (95% CI)	1.42 (0.47–4.33)			
Cox-model treatment comparisons				
OLA, hazard ratio (95% CI)	0.90 (0.27–2.95)		0.67 (0.20–2.22)	–
HAL, hazard ratio (95% CI)	1.34 (0.45–4.00)			
Discontinuation of treatment for patient's decision§				
No. of patients (%)	10 (20.8)	8 (25.0)	10 (27.8)	0.81‡
OLA, odds ratio (95% CI)	0.76 (0.28–2.07)		0.75 (0.27–2.02)	–
HAL, odds ratio (95% CI)	1.02 (0.40–2.65)			
Cox-model treatment comparisons				
OLA, hazard ratio (95% CI)	0.75 (0.41–1.35)		0.61 (0.27–1.41)	–
HAL, hazard ratio (95% CI)	1.22 (0.57–2.62)			

Significant differences in bold.

ARI, aripiprazole; OLA, olanzapine; HAL, haloperidol; AP, antipsychotic; ITT, intention to treat.

*Mean of the mean dose per patient.

†Median of the mean dose per patient.

‡Overall logistic regression.

§Missing information on reasons for drug discontinuation: four patients in aripiprazole arm; two patients in olanzapine arm.

analyses, without finding any difference from the main results.

A further explanation is that the positive effect of aripiprazole on metabolic parameters was tempered by its lower treatment retention, due to its lack of efficacy. Actually, a substantial proportion of patients in the aripiprazole's arm were switched during follow-up to other APs likely to worsen their metabolic parameters.

As in previous independent pragmatic studies, an interesting result is that an old drug such as haloperidol worked better than the latest AP aripiprazole and just as well as the newer and widely appreciated olanzapine (10,11). Dosage could have been a factor in the good performance of haloperidol. The daily mean median dose was 3 mg which is below the defined daily dose (8 mg/day) and under the lowest end of suggested range of 5–10 mg/day (41). Low dosage of haloperidol was associated with a low rate of prescription of antiparkinson drugs, a proxy indicator of extrapyramidal effects. In all trials comparing haloperidol with other APs, the average daily dose range was 4–30 mg, and in most studies, it was above 10 mg (42). This is consistent with earlier observations that haloperidol's comparative effectiveness would have been better with lower doses (43).

Jin et al. (44) recently published the first trial comparing atypical APs, including aripiprazole, in terms of MS onset. Although their findings are not directly comparable with ours, because of the different study design and the inclusion of a mix of diagnoses, the incidence of MS was 37% for patients on aripiprazole and was higher than olanzapine. Another trial comparing the effect of switching to aripiprazole vs. to stay on other SGAs

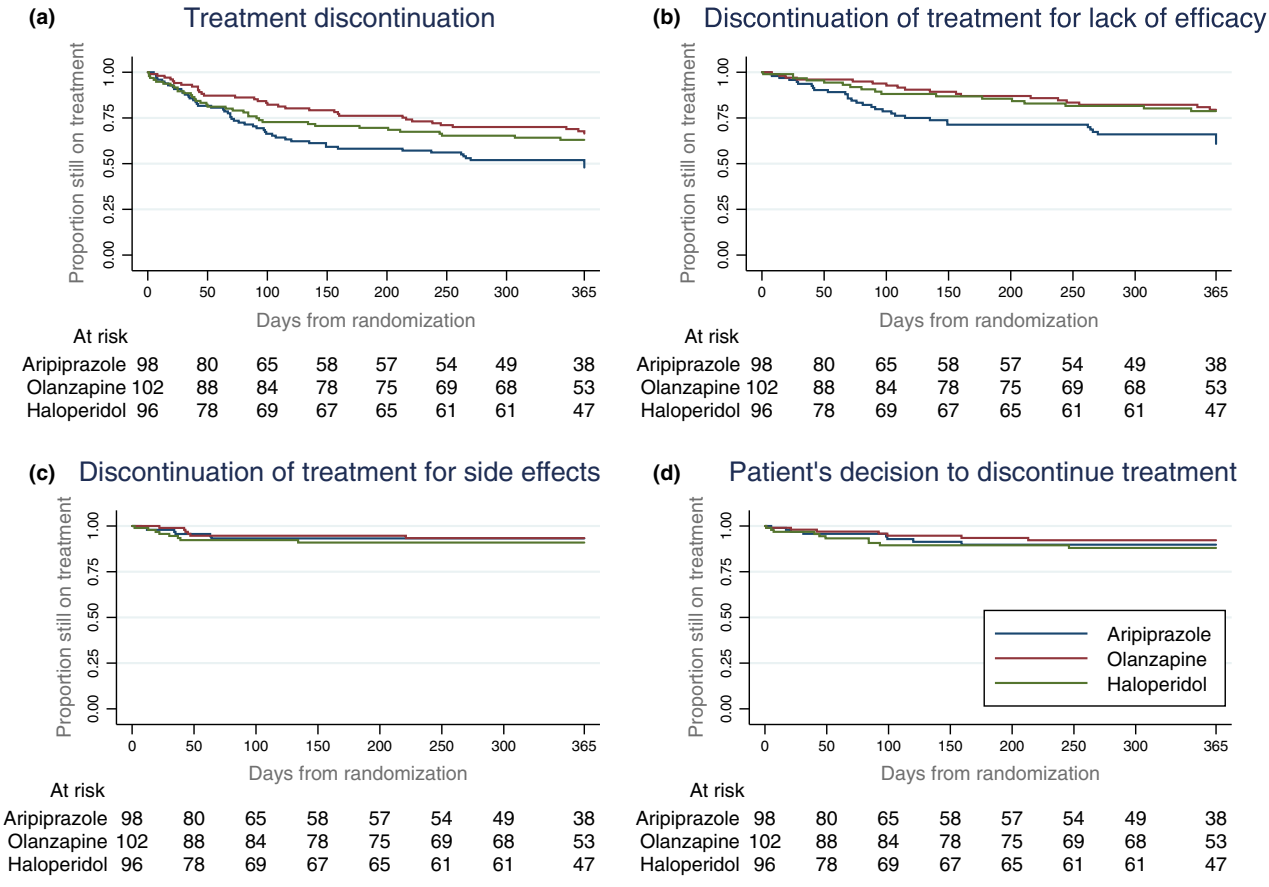


Fig. 2. Time to treatment discontinuation (a) for any cause, (b) for lack of efficacy, (c) for side effects, and d) for patient's decision in people assigned to aripiprazole (in blue), olanzapine (in red), and haloperidol (in green) (300).

showed for switchers an improvement in metabolic side-effects but with a higher 24-week discontinuation rate (45). The same authors found that switching from olanzapine to aripiprazole was not associated with any benefit in the long-term risk of MS (46).

Three schizophrenia trials compared 1-year discontinuation rates of aripiprazole with olanzapine or haloperidol, all showing higher rates for aripiprazole (47–49). Our results are particularly consistent with Kasper et al. (47) and Fleischhacker et al. (48). who reported, respectively, 57% and 59% discontinuation rates for aripiprazole. Chrzanowski et al. (49) reported a lower proportion (36%).

While the explanatory approach to clinical trials emphasizes acquiring valid information, the pragmatic approach focuses on realistically informing decisions. Our results highlighted some practical problems associated with the prescription of aripiprazole (i.e., higher rates of drug discontinuation associated with an insufficient advantage in terms of metabolic side-effects) that could have an important role in driving decisions in routine clinical practice. However, clinicians should be aware that an explanatory interpretation of our findings might be misleading. In fact, the study results cannot strictly isolate the true effect of aripiprazole consumption and are bound to data imperfection arising from non-adherence with study protocol.

In conclusion, aripiprazole cannot be considered the safest and most effective alternative for maintenance therapy of people with long-term schizophrenia in routine psychiatric services, although it may have a place in antipsychotic treatment. The choice of a drug for this population rests on careful individual assessment of the risk/benefit balance. The high 1-year incidence of MS should be a matter for concern for mental health services and confirms that the prevention of metabolic risks associated with AP use should be a primary and still neglected focus of long-term treatment of schizophrenia.

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AP, BD, MT, and AB designed the study. MT was the trial statistician, who generated the randomization list; he did the statistical analyses and advised on all statistical aspects. AP, BD, MT, and AB interpreted the results. AP and AB wrote the first draft of the manuscript and, after revision, all authors approved the final manuscript. The Steering Committee approved the study protocol, the Executive Committee supervised the trial's implementation, and the Study Team managed the trial. The Study Investigators enrolled patients. The views and opinions expressed in this manuscript are those of the authors and do not necessarily reflect those of the Italian NHS. All authors affirm that the manuscript is an accurate and transparent account of the study, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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Declaration of interest

All authors declare that they have no competing interests and that they have no past, current, or pending financial link to any organization other than the support obtained from Bristol-Myers Squibb for the present study and administered by Mario Negri Institute.

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