The GiSAS study:
Results of a pragmatic randomized controlled trial
on aripiprazole, olanzapine and haloperidol in treatment of schizophrenia

Antipsychotic drugs (AP) are a mainstay of treatment for schizophrenia[1], although recent studies casted doubts on their effects on recovery[2]. Short-term benefits of First-generation APs (FGAs) in controlling positive symptoms, though with high rates of extrapyramidal side effects[3], are well documented. However, few long-term data are available and there is no convincing evidence of their effects on negative symptoms[4,5]. Second-generation APs (SGAs) claimed to be more effective and safe than FGAs, but although inducing fewer extrapyramidal symptoms they have not yet showed clear advantages[6]. Moreover, they can cause serious weight gain and alter lipid and glucose metabolism[7].

There are actually some significant differences between APs[8,9] but they are robust only in terms of side-effects, and small in efficacy. Thus, they should be considered as an heterogeneous mix of compounds with nothing that clearly distinguishes two different classes[10]

A critical issue in research on APs is that most trials have been conducted by drug companies for registration purposes and concerned efficacy and not effectiveness. These were explanatory trials most likely set up for the success of the sponsored drugs and recruited highly selected samples[11], making comparisons uneven and limiting the external validity of the results.

The need to further investigate the effectiveness of both FGAs and SGAs in schizophrenia through large, pragmatic and independent trials has been met so far by only five major studies[12-16]. A recent review of those studies concluded that no clear advantage of one class of drugs over the other emerged and that effectiveness research in this field is still sparse and inconclusive[17]. Yet, the findings of those trials have contributed to important changes in treatment recommendations. SGAs are no more the undisputed first-line treatment and the question revolves around the relative side effect risks of FGAs and specific SGAs[18,19].

Unresolved issues related to antipsychotic drug treatment are confirmed by the high rates of treatment discontinuation and switch reported in naturalistic studies[20,21]. Inconclusive findings and conflicting views call for more pragmatic evidence to guide clinicians. Therefore, the Italian Group for the Study of Second-Generation Antipsychotics (GiSAS) designed a pragmatic trial aimed at comparing old and new antipsychotics in an unselected sample of people with schizophrenia[22].

The GiSAS trial was independently sponsored by the IRCCS 'Mario Negri' Institute for Pharmacological Research which received an unconditional grant from Bristol-Myers Squibb[22].

The study goal was to compare the overall effects of aripiprazole, the latest marketed SGA in Italy, with two well known drugs with different pharmacological profiles: haloperidol and olanzapine.

Preliminary opinions on efficacy and tolerability of aripiprazole were optimistic[23]. However, aripirazole has never been included in any major effectiveness trial and information on comparisons with other APs is inconclusive and of limited quality, thus being problematic to apply[24-26].

To address this gap, the GiSAS trial aimed to produce clinically relevant information. It was designed as 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 by considering two endpoints: the onset of metabolic syndrome (MS) and the discontinuation of treatment. The study hypothesis is that the prescription of aripiprazole, compared with olanzapine and haloperidol, is associated with lower frequency of MS and with a better drug retention, considered as a proxy for effectiveness[12].

Methods

Study design

This was an independently funded, pragmatic, multicenter, open-label, parallel-group randomized controlled trial rooted in everyday clinical practice. The study rationale and protocol have been described in detail[22]. The aim was to evaluate over one year the safety and effectiveness of aripiprazole, olanzapine and haloperidol for patients with schizophrenia. To enhance representativeness, the inclusion criteria were wide and recruitment took place in a broad array of settings. The sample was meant to be heterogeneous and to reflect the real population attending psychiatric services, including those with comorbid conditions. The study did not replace any aspect of the usual clinical care. The participants were seen as often as indicated and all examinations have been performed by the treating teams, with the exception of the centralized analyses of blood samples performed to detect metabolic disturbances at follow-up.

The research 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 initially planned sample size of 250 patients per arm and to prolong recruitment[22].

Participants

Forty-three centres (7 medical schools and 36 National Health Service Mental Health Departments) in 14 out of the 20 Italian regions were recruited. Clinicians were asked to screen for eligibility all

patients with age over 18 years and a DSM IV diagnosis of schizophrenia based on the Mini-International Neuropsychiatric Interview[7], and to evaluate the opportunity to start or change treatment with an oral AP. Exclusion criteria were: 1) diagnosis of MS, assessed by the treating clinician and defined as at least three of the five criteria indicated by the Adult Treatment Panel III (ATP III)[28]: 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 mm Hg or on antihypertensive medication); hyperglycemia (fasting glucose ≥110 mg/dl or on insulin or hypoglycemic medication; 2) diagnosis of diabetes mellitus type II; 3) specific contraindications to one of the study drugs (including evidence from patient's medical history of the ineffectiveness or intolerability of one of the study drugs); 4) no previous exposition to APs.

Patients were recruited in any clinical setting: community-based mental health centers, general hospital inpatient units, short and long-term residential facilities and day centers. Patients considered for inclusion, or their legal representatives, were asked to provide informed consent and then enrolled. In eight centres clinicians could not identify any suitable patient. Thus, patients were recruited from 35 mental health services.

Procedures

Eligible patients were randomized in a 1:1:1 ratio to non-blind oral monotherapy with one of the three study drugs. The computer-generated allocation sequence was site-stratified and in blocks. First block of randomization was of size 9, followed by blocks of 3. Investigators were kept unaware of the randomization scheme. Concealment was achieved via a central randomization by telephone with an interactive voice response system.

All people involved in the trial's coordination, in the primary outcome assessment and in data analysis were blinded. Masking was maintained by omitting in report forms any clue that could reveal the study drug and by using a masked code for treatment groups in all analyses. Blood tests for metabolic parameters were performed in an unique and independent reference laboratory. Test results were registered with different codes into a separate database. All data were examined after the study database was locked. Analyses were performed by a separate unit whose personnel was not involved in the study conduction. The randomization code was broken at the end of the study and after the primary analysis.

The three study drugs were marketed in Italy for the treatment of schizophrenia. After randomization, the assigned drugs were prescribed according to usual practice and adjusted according to individual response. After inclusion no limits were imposed to the clinicians who were free to treat patients at their own discretion. The use of concomitant psychotropic or non-

psychotropic medication was allowed and recorded. The use of concomitant APs, although allowed, was considered treatment failure.

Included subjects were assessed at baseline, when monotherapy treatment was discontinued, and at 12 months. Clinicians were regularly prompted to monitor adherence and to register changes in the prescriptions. Reasons for discontinuation were collected. Information on psychosocial interventions and hospital or residential admissions were drawn from patient records at follow-up. The study was realized according to good clinical practice European standards[29] and its phases were recorded following the CONSORT statement, as modified for reporting of pragmatic trials[30,31].

Outcome measures

The proportion of subjects who developed MS at one year was the primary endpoint, the one-year discontinuation of the allocated monotherapy was the main secondary endpoint.

MS was defined as the fulfilling of at least three of the already mentioned diagnostic criteria[27]. All-cause discontinuation was considered treatment failure. Switching to another AP, adding a second AP or stopping the assigned drug were defined as discontinuation. Discontinuers counted as treatment failures but were followed-up for the rest of the study period as well. The proportion of subjects who discontinued treatment at one year was compared between the study arms. Time to discontinuation and reasons for discontinuing were taken into account in the secondary analyses. Drug discontinuation for clinical remission was not considered as a treatment failure.

Other secondary endpoints were Global Assessment of Functioning score[32] and patients' subjective assessment of adverse effects, measured by the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)[33].

Statistical analysis

Centres with less than 9 patients were grouped on a geographical basis. The analyses of the primary outcome were performed on the following populations: a) intention-to-treat population (the primary analysis population: all randomized patients); b) per-protocol population (patients who were confirmed free from MS at baseline by centralized analyses and took at least 30 days of the allocated treatment); c) completers population (patients who had complete metabolic parameters at follow-up); d) compliers-completers population (patients who had complete metabolic parameters and were still on the allocated monotherapy treatment at follow-up). Analyses comparing differences in the proportion of subjects who discontinued treatment at one year, and in time to discontinuation were performed only on the intention-to-treat population.

The first step of the primary analysis was an overall logistic regression taking into account the stratification criterion used ($p \leq 0.05$, two-tailed). In the second step, pairwise comparisons

between aripiprazole and olanzapine, and aripiprazole and haloperidol were performed using a Hochberg adjustment for multiple comparisons.

Analyses with replacement of missing data were performed on the intention-to-treat and the per-protocol populations. A method based on direct imputation was followed by multiple imputations (MI). In the primary analysis when, at treatment discontinuation, the complete set of MS parameters was available a last observation carried forward (LOCF) approach was used, otherwise a worst outcome approach (WO) was used. To confirm the primary results two approaches were followed: a) only MI, and b) MI or direct imputation in patients for whom information on hypertension and waist-to-height ratio was available. In this last case, the diagnosis of MS was derived from the following criteria: waist-to-height ratio (WHtR) ≥0.56 in men and ≥0.54 in women and hypertension[33]. MI was performed on a single multivariate step, separately by treatment group. Since no multivariate normality could be assumed, a bootstrap method was used. Baseline variables with a low number of missing values were chosen as regressors (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, other two secondary MI analyses were performed: analysis on complete dataset with MI imputation with the above variables (starting with age and sex only on the independent side of the imputation process); direct imputation of outcome (presence/absence of MS).

Time to discontinuation was defined as the number of days between the date of randomization and date of drug discontinuation. For the analysis on proportions the method of the primary analysis was replicated. Differences in time to discontinuation between aripiprazole and olanzapine or haloperidol were evaluated using Cox proportional hazards models and log-rank tests ($p \leq 0.05$) with same Hochberg adjustment described above.

Data checking and handling were performed with JMP Pro v 10.0 (SAS Institute Inc., Cary, NC). Analyses were performed with Stata v 12.1 (StataCorp, College Station, TX).

Sample size and power

We estimated the risk of developing MS as follows: 25% in the olanzapine group, 20% in the haloperidol group and 5% in the aripiprazole group. We calculated that a sample of 80 subjects per arm would have had a power of 77% to detect a difference of 15% between aripiprazole and haloperidol (at $p=0.05$), and a power of 87% to detect a difference of 20% between aripiprazole and olanzapine (at $p=0.025$). The comparison between olanzapine and haloperidol was considered as a secondary endpoint. A sample size of 240 subjects had a power of 89% to yield a statistically significant result. Assuming a dropout rate of 10%, 264 subjects were required.

Results

Patient flow and characteristics

The study recruitment lasted from October 2007 to June 2011. **Figure 1** shows the patients' progress through the trial. 1261 patients were assessed for eligibility. Of these, 961 (76%) could not be included: 667 (53%) because did not meet inclusion criteria; 55 (4%) because refused to give consent; 239 (19%) for other reasons. Most patients not meeting inclusion criteria were not included because changing current antipsychotic treatment was considered inappropriate (n=476; 71%). 300 subjects were randomized by 76 investigators, 100 to aripiprazole, 103 to olanzapine, 97 to haloperidol.

Figure 1 around here

The main characteristics of the three groups are shown in **Table 1**. Before randomization, 75% of the sample had taken only oral APs, and 6% had not taken any antipsychotic. Forty-one patients (14%) had taken depot FGAs and 8 (3%) had taken depot SGAs.

Table 1 around here

Eighty-two (33%) patients had taken oral FGAs and 195 (79%) were taking 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.

Aripiprazole had been prescribed before randomization to 24 (10%) patients, olanzapine to 78 (31%), and haloperidol to 63 (25%). Thus, 165 (55%) patients had one-third chance of being randomized to continue baseline treatment and 68 (23%) were randomized to the same drug prescribed before entering the study. Adherence to previous AP medication regimens was rated as satisfactory by the treating clinicians of 207 (69%) patients, 194 (64%) patients had positive attitudes towards AP efficacy, 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.

Metabolic syndrome

Table 2 shows the primary ITT analysis of the difference in the proportions of patients found positive for MS at one year, including results from multiple imputation of missing data, and the secondary analyses of the same outcome on the other study populations. The one-year prevalence of MS was 37% (aripiprazole), 47% (olanzapine), and 42% (haloperidol) after direct imputation of missing values (i.e. primary ITT analysis), it was 20% (aripiprazole), 28% (olanzapine), and 26% (haloperidol) after direct imputation of a surrogate diagnosis of MS and MI, and 18%

(aripiprazole), 30% (olanzapine), and 25% (haloperidol) in complete cases. No significant differences were found among treatments groups in the primary and secondary analyses. Moreover, in the ITT population, no significant differences were found in the secondary pair-wise comparisons (**Table 3**).

Table 2 around here

Table 3 around here

Discontinuation of treatment

The mean median doses were 20 mg per day for aripiprazole, 10 mg per day for olanzapine, and 3 mg per day for haloperidol. The proportion of patients who discontinued treatment for any cause was higher in the aripiprazole group (52%) than in the olanzapine group (33%; odds ratio, 0.41; p=0.004), and the haloperidol group (37%; odds ratio, 0.51; p=0.030). No significant difference was found between the olanzapine and the haloperidol (odds ratio 0.81; p=0.493).

One subject, in the haloperidol group, discontinued treatment for clinical remission.

Table 4 around here

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 (hazard ratio, 0.67; p=0.094), or between olanzapine and haloperidol (hazard ratio, 0.82; p=0.514).

The rate of discontinuation for lack of efficacy was higher for aripiprazole (32%) than for olanzapine (17%; odds ratio, 0.44; p=0.017), and haloperidol (19%; odds ratio, 0.48; p=0.032). No significant difference was found between olanzapine and haloperidol (odds ratio 0.92; p=0.826).

The time to discontinuation for lack of efficacy was longer in the olanzapine group than in the aripiprazole group (hazard ratio, 0.46; p=0.001). No significant differences were found between haloperidol and aripiprazole (hazard ratio 0.50; p=0.058), or between olanzapine and haloperidol (hazard ratio, 0.92; p=0.787).

There were no significant differences between groups in the proportion of patients who discontinued treatment for side-effects (p=0.758) or for independent decision (p=814).

Other secondary outcomes

The GAF scores improved over time in all groups ($p<0.05$) with no statistical significant differences between groups at both drug discontinuation ($p=0.318$) and follow-up (0.837) (**Table 4**).
The total LUNSERS scores improved over time in all groups ($p<0.05$) with no statistical significant differences between groups at both drug discontinuation ($p=0.890$) and follow-up (0.845) (**Table 4**).
The rates of adverse events and side effects are listed in **Table 1 of supplementary materials**. Overall, they were very few and no difference between groups was observed. One patients from each treatment died for reasons not attributable to trial participation.

Discussion

The results of this pragmatic trial rejected the hypothesis that the prescription of aripiprazole was associated to a lower occurrence of MS in comparison with olanzapine and haloperidol. Moreover, retention on treatment with aripiprazole was worse than with olanzapine and haloperidol. Higher rates of drug discontinuation in aripiprazole's arm were ascribed by the clinicians to lack of efficacy.
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%). Was the proposed difference unrealistically large? Given the observed rate of MS in the olanzapine's arm, a difference of 20% would correspond to a number needed to treat of 6 patients (or a small to medium effect size) which is a reasonable clinical aim [*].
The second possibility is that sample size and statistical power were too small. However, given the above rate of MS in the olanzapine's arm, the recruited sample had an adequate 77% power to detect the hypothesized difference with aripiprazole.
Third, we have to consider limits in the study design or implementation. Namely, the absence of blinding and the missing follow-up data. The open nature of the study should not be considered a weakness. It enhanced its feasibility and reflected real clinical practice, thus increasing the 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 exact intervention patients would have received in real world, and this moved our trial toward the pragmatic side of the pragmatic-explanatory continuum [**]. Knowing to which drug a subject was assigned could not have influenced the primary endpoint of this trial. However, as it could have influenced drug retention, we will explore the possible effect of clinicians expectations on this outcome in a future analysis [***]. Due to missing data we could not formulate an ATP-III diagnosis of MS at one year for one third of the sample. However, only 12% of the patients were actually lost to follow-up. For the other 18% of the sample only part of the full set of MS components was missing, with reasons

suggesting they were missing completely at random. All available options for dealing with missing data were explored and a number of adequately powered sensitivity analyses were performed without finding any difference with the main results.
The fourth explanation is that the positive effect of aripiprazole on metabolic parameters was tempered by its lower treatment retention. About half of the patients in ariprazole arm, in fact, were switched to other antipsychotics during follow-up and this could have contributed to worsen their metabolic profiles. This circumstance was of course contemplated by the study protocol.

As in previous independent pragmatic research, one of the most interesting results of this study is that an old drug like haloperidol worked better than the latest antipsychotic aripiprazole and as well as the newer and widely appreciated olanzapine [12, 13]. Dose could have been a factor in the good performance of haloperidol. Its daily mean median dose was 3 mg which is quite below the drug's defined daily dose (i.e. 8 mg/day) and at the lowest end in the suggested dose range of 3-10 mg/day. This is consistent with the hypothesis by Geddes and colleagues (2000) that haloperidol's comparative effectiveness would have improved with lower doses [****].
The 1-year discontinuation rate of 52% for aripiprazole found in our study is similar to the 57% found by Kasper et al. in comparison with haloperidol and 59% by Fleischhacker et al. in comparison with olanzapine

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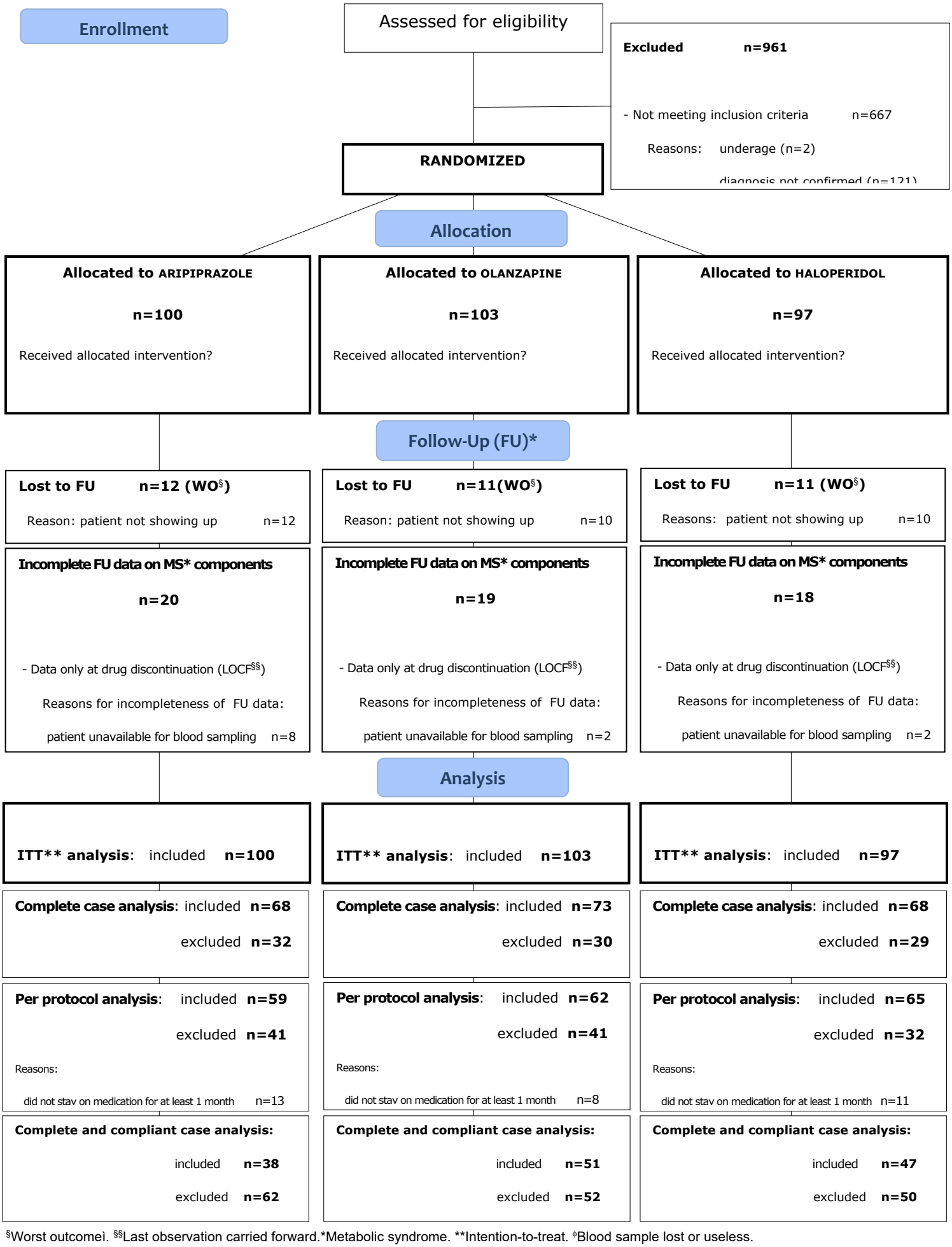


§Worst outcome). §§Last observation carried forward.*Metabolic syndrome. **Intention-to-treat. ϕBlood sample lost or useless.

Figure 1. CONSORT Diagram: progress of the randomised patients through the study.

	Aripiprazole (n=100)	**Olanzapine** (n=103)	**Haloperidol** (n=97)	**All subjects** (n=300)

Socio-demographic characteristics								
Sex, n (%)								
M	55	(55)	66	(64)	54	(56)	175	(58)
F	45	(45)	37	(36)	43	(44)	125	(42)
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)
Missing	3	(3)	1	(1)	2	(2)	6	(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)
Missing	10	(10)	15	(15)	5	(5)	30	(10)
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)
Missing	20	(20)	13	(13)	15	(16)	48	(16)
Years from first contact with recruiting center, n (%)								
0-2 years	37	(37)	27	(26)	32	(33)	96	(32)
3+ years	52	(52)	65	(63)	57	(59)	174	(58)
Missing	11	(11)	11	(11)	8	(8)	30	(10)
Patient status at baseline, n (%)								
Inpatient	20	(20)	15	(15)	25	(26)	60	(20)
Outpatient	76	(76)	87	(85)	69	(71)	232	(77)
Missing	4	(4)	1	(1)	3	(3)	8	(3)
Current substance abuse or dependence, n (%)								
Yes	9	(9)	2	(2)	4	(4)	15	(5)
No	86	(86)	100	(97)	92	(95)	278	(93)
Missing	5	(5)	1	(1)	1	(1)	7	(2)
Tardive dyskinesia, n (%)								
Yes	0	(0)	0	(0)	1	(1)	1	(0)
No	97	(97)	101	(98)	95	(98)	293	(98)
Missing	3	(3)	2	(2)	1	(1)	6	(2)
Lifetime suicide attempts, n (%)								
Yes	21	(21)	13	(13)	10	(10)	44	(15)
No	76	(76)	87	(84)	86	(89)	249	(83)
Missing	3	(3)	3	(3)	1	(1)	7	(2)
Baseline clinical characteristics								
Weight (Kg)								
Mean (SD)	73.2	(14.3)	76.8	(16.0)	76.0	(14.5)	75.4	(15.0)
Missing, n (%)	4	(4)	1	(1)	1	(1)	6	(2)
Waist circumference (Wt), cm								
Mean (SD)	92.7	(15.2)	96.6	(14.4)	95.3	(15.3)	94.9	(15.0)
Missing. n (%)	4	(4)	4	(4)	3	(3)	11	(4)
Waist-to-height ratio (WtHtR)								
Mean (SD)	0.6	(0.1)	0.6	(0.1)	0.6	(0.1)	0.6	(0.1)
Missing, n (%)	4	(4)	4	(4)	3	(3)	11	(4)
Diastolic blood pressure								
Mean (SD)	78.1	(7.6)	78.9	(7.8)	79.1	(7.3)	78.7	(7.6)
Missing, n (%)	6	(6)	2	(2)	3	(3)	11	(4)

Systolic blood pressure								
Mean (SD)	123.4	(13.5)	122.0	(11.6)	123.5	(11.1)	123.0	(12.1)
Missing,n (%)	6	(6)	2	(2)	3	(3)	11	(4)
QTc								
Mean (SD)	398.6	(29.8)	395.6	(31.3)	397.6	(36.2)	397.2	(32.5)
Missing, n (%)	11	(11)	11	(11)	4	(4)	26	(9)
QTc classes, n (%)								
Short	31	(31)	33	(32)	35	(36)	99	(33)
Normal	49	(49)	47	(46)	40	(41)	136	(45)
Borderline	5	(5)	11	(11)	12	(12)	28	(9)
Prolonged	4	(4)	1	(1)	5	(5)	10	(3)
Critical	0	(0)	0	(0)	1	(1)	1	(0)
Missing	11	(11)	11	(11)	4	(4)	26	(9)
BPRS total score								
Mean (SD)	58.1	(17.1)	57.1	(20.0)	57.9	(19.6)	57.7	(18.9)
Missing, n (%)	4	(4)	1	(1)	1	(1)	6	(2)
GAF score								
Mean (SD)	47.5	(13.8)	48.6	(16.1)	50.2	(15.2)	48.8	(15.1)
Missing, n (%)	4	(4)	2	(2)	1	(1)	7	(2)
LUNSERS score								
Mean (SD)	27.9	17.4	28.8	16.8	30.0	19.0	28.9	17.7
Missing, n (%)	11	(11)	11	(11)	12	(12)	34	(11)

Table 1. Baseline socio-demographic and clinical characteristics of randomized patients by treatment arm.

	Aripiprazole (n=100)		Olanzapine (n=103)		Haloperidol (n=97)		All subj (n=30	
treatment before randomization								
e of medication, no (%)								
Oral AP	80	(80)	76	(74)	69	(71)	225	
Depot	4	(4)	15	(15)	7	(7)	26	
Both	7	(7)	4	(4)	12	(12)	23	
None	5	(5)	5	(5)	8	(8)	18	
Missing	4	(4)	3	(3)	1	(1)	8	
l AP, n (%)*								
Amisulpride	2	(2)	2	(3)	0	(0)	4	
Aripiprazole	11	(13)	7	(9)	6	(7)	24	
Bromperidol	1	(1)	2	(3)	0	(0)	3	
Chlorpromazine	0	(0)	1	(1)	0	(0)	1	
Clotiapine	1	(1)	2	(3)	1	(1)	4	
Clozapine	5	(6)	4	(5)	5	(6)	14	
Haloperidol	22	(25)	16	(20)	25	(31)	63	
Levomepromazine	1	(1)	0	(0)	1	(1)	2	
Olanzapine	30	(34)	32	(40)	16	(20)	78	
Paliperidone	1	(1)	0	(0)	2	(2)	3	
Penfluridol	0	(0)	1	(1)	0	(0)	1	
Perphenazine	0	(0)	0	(0)	2	(2)	2	
Pimozide	1	(1)	0	(0)	0	(0)	1	
Promazine	0	(0)	2	(3)	1	(1)	3	
Quetiapine	8	(9)	6	(8)	9	(11)	23	
Risperidone	16	(18)	15	(19)	18	(22)	49	
Zuclopenthixol	0	(0)	0	(0)	2	(2)	2	
ot AP, n (%)								
Fluphenazine decanoate	4	(36)	3	(16)	5	(26)	12	
Haloperidol decanoate	6	(55)	11	(58)	10	(53)	27	
Zuclopenthixol decanoate	1	(9)	1	(5)	0	(0)	2	
Risperidone long-acting	0	(0)	4	(21)	4	(21)	8	
erence to previous AP treatments (clinician rated), n (%)								
Unsatisfactory	5	(5)	7	(7)	5	(5)	17	
Uncertain	22	(22)	20	(19)	19	(20)	61	
Satisfactory	65	(65)	72	(70)	70	(72)	207	
Not evaluable	5	(5)	3	(3)	2	(2)	10	
Missing	3	(3)	1	(1)	1	(1)	5	
nion on efficacy of previous AP treatments (patient rated), n (%)								
Very negative	1	(1)	3	(3)	0	(0)	4	
Somehow negative	28	(28)	24	(23)	26	(27)	78	
Somehow positive	44	(44)	55	(53)	55	(57)	154	
Very positive	16	(16)	13	(13)	11	(11)	40	
Not evaluable	8	(8)	6	(6)	4	(4)	18	
nion on tolerability of previous AP treatments (patient rated), n (%)								
Very negative	2	(2)	0	(0)	2	(2)	4	
Somehow negative	33	(33)	24	(23)	29	(30)	86	
Somehow positive	44	(44)	60	(58)	51	(53)	155	
Very positive	10	(10)	8	(8)	7	(7)	25	
Not evaluable	8	(8)	10	(10)	7	(7)	25	

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

Table 2. Antipsychotic (AP) medications before randomization, clinicians' opinion on adherence to previous AP treatments, and patients' opinion on the efficacy and tolerability of previous AP treatments by treatment arm.

			ARI		OLA		HAL		P value*
Direct imputation 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)	0.38
PP secondary analysis	patients	n	59		62		66		
	MS at 1 year	n (%)	15	(25.4)	22	(35.5)	22	(33.3)	0.45
Multiple imputation of missing values									
ITT secondary analyses									
Only MI	patients	n	100		103		97		0.40
	MS at 1 year	n (%)	23	(23.2)	32	(30.7)	28	(28.4)	
Direct imputation of WHtR and MI	patients	n	100		103		97		0.49
	MS at 1 year	n (%)	20	(20.0)	28	(27.7)	25	(25.6)	
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)	0.22
CCC secondary analysis	patients	n	38		51		46		
	MS at 1 year	n (%)	6	(15.8)	15	(29.4)	10	(21.7)	0.22

*Overall logistic regression;**direct imputation of LOCF and WO data. Significant differences in bold.
Abbreviations: 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; WHtR, waist-to-height ratio.

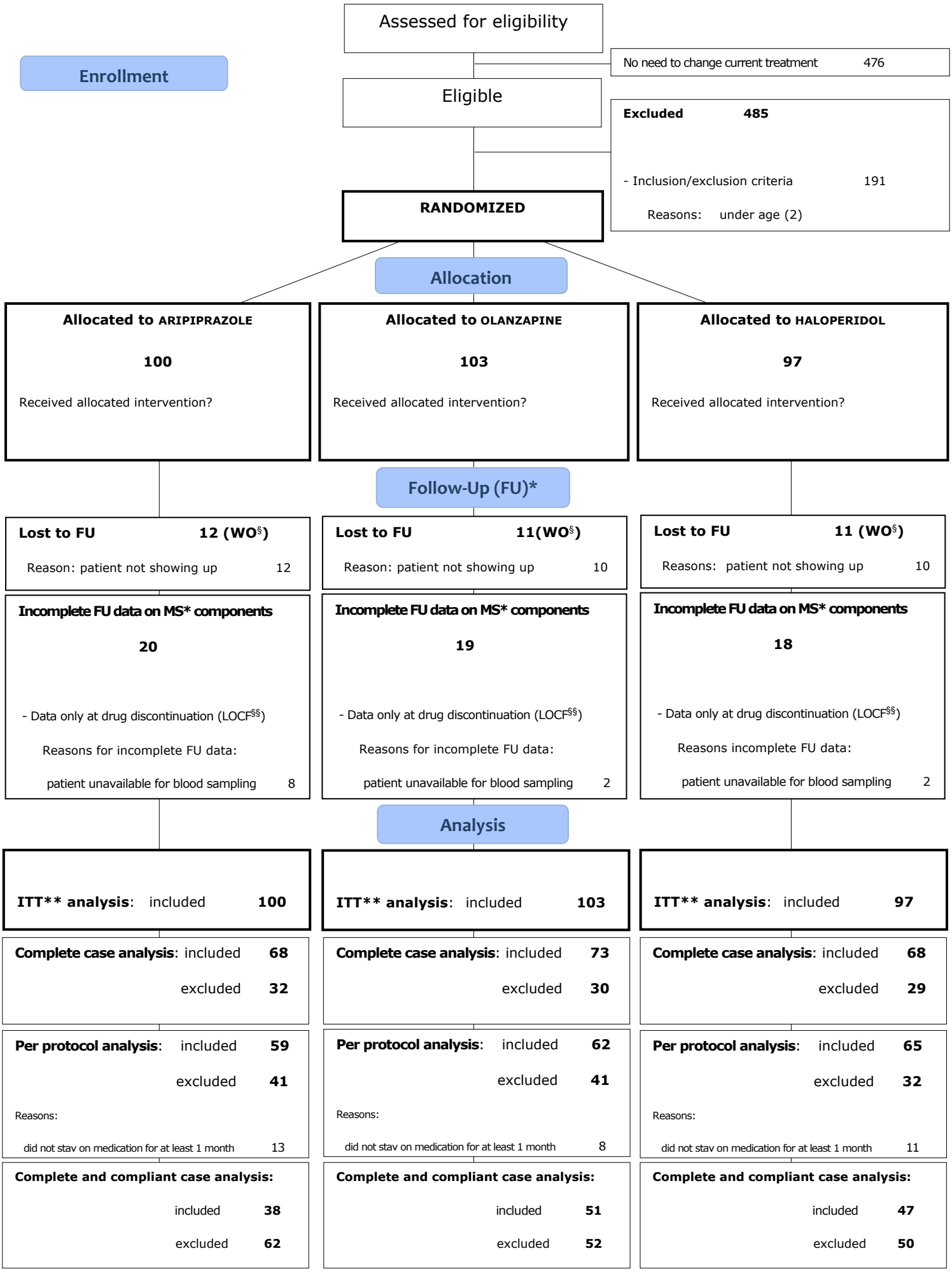
Table 3. Primary ITT, secondary ITT and sub-population analyses on the difference in the one-year proportion of patients found positive for MS.

	ARI		OLA	
Treatment, mg/day				
Mean[¥] (SD)	19.75	(8.73)	13.72	(5.61)
Median[¥¥] (25^{th}-75^{th} percentile)	20.00	(11-30)	10.00	(10-20)
Global functioning and symptomatology (GAF score)				
At drug discontinuation				
No. subjects with missing data (%)	10	(20.8)	7	(21.9)
Mean (SD)	43.50	(15.16)	44.84	(17.19)
At 12 months				
No. subjects with missing data	23	(23.0)	14	(13.6)
Mean (SD)	58.47	(15.02)	57.21	(17.04)
Discontinuation of treatment for any cause				
Discontinuation, no. of patients (%)	52	(52.0)	34	(33.0)
OLA, odds ratio (95% CI)	**0.41**	**(0.23-0.76)**		
HAL, odds ratio (95% CI)	**0.51**	**(0.28-0.94)**		
Kaplan–Meier time to discontinuation (days), 75^{th} percentile (95% CI)	70	(40-99)	216	(99-365)
Cox-model treatment comparisons				
OLA, hazard ratio (95% CI)	**0.55**	**(0.42-0.73)**		
HAL, hazard ratio (95% CI)	0.67	(0.42-1.07)		
Discontinuation of treatment for lack of efficacy*				
Discontinuation, no. of patients (%)	32	(66.7)	18	(56.3)
OLA, odds ratio (95% CI)	**0.44**	**(0.23-0.86)**		
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)**		
HAL, hazard ratio (95% CI)	0.50	(0.24-1.03)		
Discontinuation of treatment for side effects*				
Discontinuation, no. of patients (%)	6	(12.6)	6	(18.8)
OLA, odds ratio (95% CI)	0.98	(0.30-3.19)		
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)		
HAL, hazard ratio (95% CI)	1.34	(0.45-4.00)		
Patient's decision to discontinue treatment*				
Discontinuation, no. of patients (%)	10	(20.8)	8	(25.0)
OLA, odds ratio (95% CI)				
HAL, odds ratio (95% CI)	0.76	(0.28-2.07)		
	1.02	(0.40-2.65)		
Cox-model treatment comparisons				
OLA, hazard ratio (95% CI)	0.75	(0.41-1.35)		
HAL, hazard ratio (95% CI)	1.22	(0.57-2.62)		

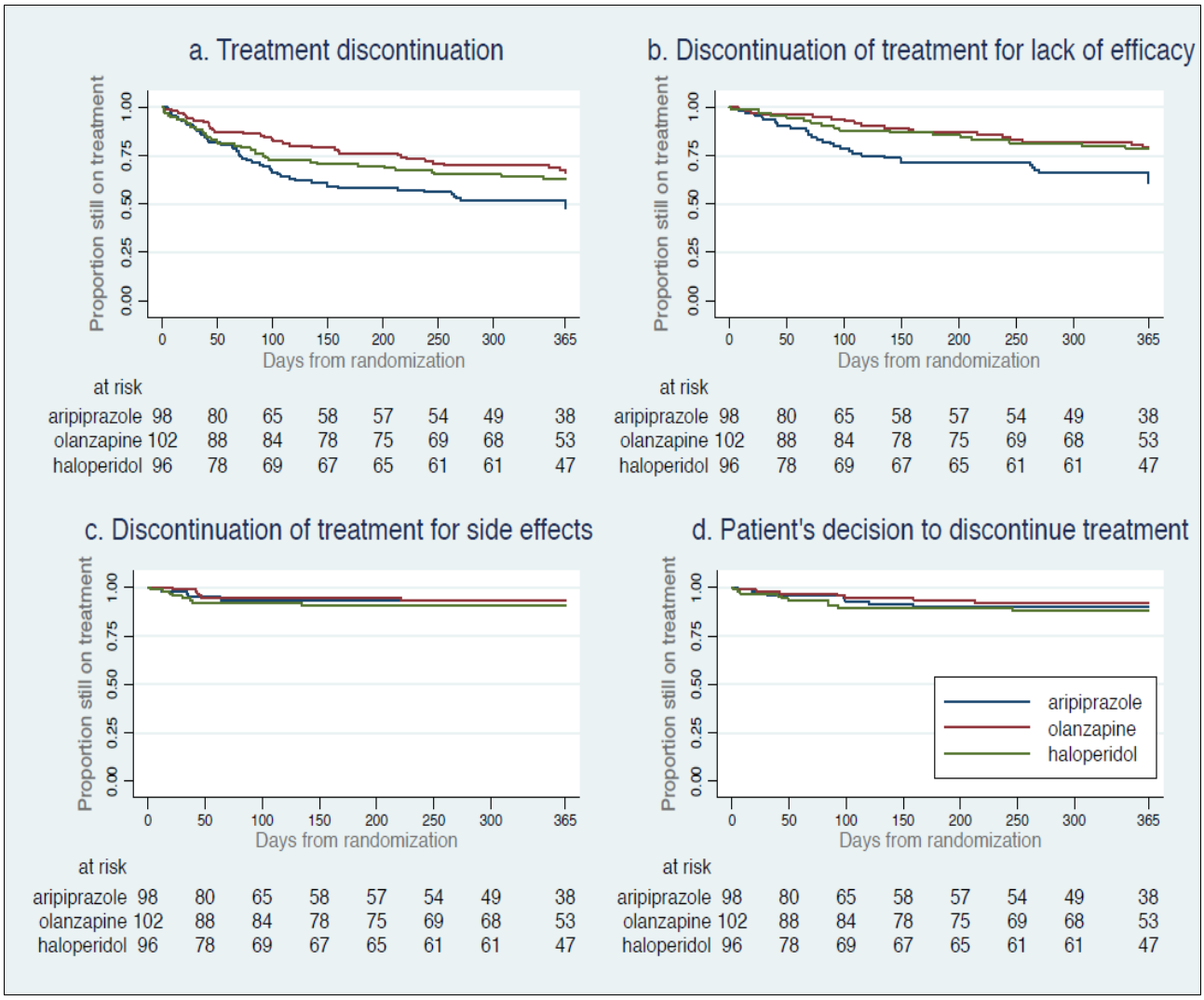
[¥]Mean of the mean dose per subject; [¥¥]Median of the mean dose per subject; [§]Overall logistic regression
*missing information on reasons for drug discontinuation: 4 subjects in aripiprazole arm; 2 subjects in olanzapine arm.
Abbreviations: ARI, aripiprazole; OLA, olanzapine; HAL, haloperidol.
Significant differences in bold.

Table 4. Outcome measures of effectiveness in the intention-to-treat (ITT) population (n=300).



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

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).



Supplementary Table 1.

Adverse events and other outcomes for safety and tolerability in randomized patients by treatment arm.

	ARI	OLA	HAL	Total

	(100)		(103)		(97)		(300)	
One-year rates of adverse events*								
Deaths*, no. (%)	1	(1)	1	(1)	1	(1)	3	(1)
Non-psychiatric hospitalizations, no. (%)	0	(0)	0	(0)	1	(1)	1	(0)
Psychiatric hospitalizations, no. (%)	20	(20)	12	(12)	14	(14)	46	(15)
Access to day care or residential facilities, no. (%)	17	(17)	17	(17)	17	(17)	51	(17)
Abdominal obesity**, no. (%)								
Yes	29	(29)	42	(41)	34	(35)	105	(35)
No	45	(45)	46	(45)	43	(44)	134	(45)
Hypertension***, no. (%)								
Yes	28	(28)	36	(35)	42	(43)	106	(35)
No	45	(45)	48	(47)	38	(39)	131	(44)
High glucose****, no. (%)								
Yes	10	(10)	1	(1)	5	(5)	16	(5)
No	60	(60)	74	(72)	63	(65)	197	(66)
Low HDL§, no. (%)								
Yes	21	(21)	29	(28)	23	(24)	73	(24)
No	49	(49)	46	(45)	46	(47)	141	(47)
High triglycerides§§, no. (%)								
Yes	18	(18)	33	(32)	24	(25)	75	(25)
No	53	(53)	42	(41)	45	(46)	140	(47)
High waist-to-height ratio (WHtR)§§§, no. (%)								
Yes	37	(37)	54	(52)	40	(41)	131	(44)
No	37	(37)	34	(33)	37	(38)	108	(36)
Surrogate diagnosis of MS§§§§, no. (%)								
Yes	16	(16)	26	(25)	22	(23)	64	(21)
No	58	(58)	60	(58)	56	(58)	174	(58)
Significant weight gain¥, no. (%)								
Yes	18	(18)	21	(20)	11	(11)	50	(17)
No	55	(55)	67	(65)	69	(71)	191	(64)
Significant waist increase¥¥, no. (%)								
Yes	12	(12)	16	(16)	10	(10)	38	(13)
No	62	(62)	70	(68)	66	(68)	198	(66)

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	ARI (100)		OLA (103)		HAL (97)		Total (300)	
On treatment rates of adverse events								
QTc abnormalities$^{\phi}$, no. (%)								
Short QTc	28	(28)	27	(26)	19	(20)	74	(25)
Normal QTc	35	(35)	37	(36)	37	(38)	109	(36)
Borderline QTC	6	(6)	7	(7)	9	(9)	22	(7)
Prolonged QTc	4	(4)	3	(3)	2	(2)	9	(3)
ECG abnormalities$^{\phi\phi}$, no. (%)								
Yes	11	(11)	6	(6)	11	(11)	28	(9)
No	63	(63)	70	(68)	60	(62)	193	(64)
High prolactin$^{\phi\phi\phi}$, no. (%)								
Yes	12	(12)	20	(19)	21	(22)	53	(18)
No	60	(60)	56	(54)	48	(49)	164	(55)
Low neutrophil count$^{\pm}$, no. (%)								
Normal	72	(72)	77	(75)	75	(77)	224	(75)
Moderate	3	(3)	2	(2)	1	(1)	6	(2)
Severe	1	(1)	5	(5)	2	(2)	8	(3)
Hyponatraemia$^{\pm\pm}$, no. (%)								
Yes	5	(5)	2	(2)	4	(4)	11	(4)
No	65	(65)	78	76)	66	(68)	209	(70)
Hypokalaemia$^{\pm\pm\pm}$, no. (%)								
Yes	1	(1)	3	(3)	1	(1)	5	(2)
No	70	(70)	76	(74)	69	(71)	215	(72)
Hypomagnesaemia$^{\pm\pm\pm\pm}$, no. (%)								
Yes	16	(16)	16	(16)	18	(19)	50	(17)
No	21	(21)	31	(30)	27	(28)	79	(26)
High glucose***, no. (%)								
Yes	2	(2)	0	(0)	3	(3)	5	(2)
No	75	(75)	77	(75)	66	(68)	218	(73)

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(Continues from previous page)	**ARI** (100)		**OLA** (103)		**HAL** (97)		**Total** (300)	
On treatment rates of adverse events								
Akathisia¶, no. (%)								
Yes	3	(3)	3	(3)	5	(5)	11	(4)
No	78	(78)	88	(85)	77	(79)	243	(81)
Parkinsonism¶, no. (%)								
Yes	2	(2)	1	(1)	6	(6)	9	(3)
No	79	(79)	90	(87)	76	(78)	245	(82)
Dystonia¶, no. (%)								
Yes	1	(1)	0	(0)	2	(2)	3	(1)
No	80	(80)	91	(88)	80	(82)	251	(84)
Gynaecomastia¶, no. (%)								
Yes	1	(1)	0	(0)	0	(0)	1	(0)
No	80	(80)	91	(88)	82	(85)	253	(84)
Galactorrhea¶, no. (%)								
Yes	0	(0)	0	(0)	0	(0)	0	(0)
No	81	(81)	91	(88)	82	(85)	254	(85)
Dysmenorrhea¶, no. (%)								
Yes	2	(4)	1	(3)	0	(0)	3	(2)
No	38	(84)	33	(89)	36	(84)	107	(86)
Irregular menstruation¶, no. (%)								
Yes	6	(13)	2	(5)	2	(5)	10	(8)
No	34	(76)	32	(86)	35	(81)	101	(81)

Each adverse event accounted for one patient. For categorical or ordinal variables percentages do not add up to 100 because of missing data. Abbreviations: ARI, aripiprazole; OLA, olanzapine; HAL, haloperidol.

*Deaths were deemed unrelated to trial participation: 1 death caused by myocardial infarction (aripiprazole arm), 2 deaths caused by pulmonary complications of HIV infection (olanzapine and haloperidol arms); **Waist circumference >102 cm in men or >88 cm in women; ***blood pressure ≥130/85 mmHg or on antihypertensive medication (ATC classes: C02, C03, C07, C08); ****fasting glucose ≥110 mg/dL or on insulin or hypoglycemic medication (ATC class: A10); §fasting high density lipoprotein (HDL) <40 mg/dL in men or <50 mg/dL in women; §§fasting triglycerides ≥150 mg/dL; §§§waist-to-height ratio (WHtR) ≥0.56 in men and ≥0.54 in women; §§§§diagnosis of MS derived 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 (ATC classes: C02, C03, C07, C08); ¥change ≥7% from baseline; ¥¥change ≥7% from baseline; ϕQTc <390ms (short), 390ms≤QTc<430ms (normal in males) and 390ms<QTc<440ms (normal in females), 430ms≤QTc<450ms (borderline in males) and 440ms≤QTc<460ms (borderline in females), 450ms≤QTc<500ms (prolonged in males) and 460ms≤QTc<500ms (prolonged in females), QTc≥500ms (critical); ϕϕevidence of atrial fibrillation/flutter, right bundle branch block, PM-induced rhythm, left bundle branch block, pathological Q waves, and/or left ventricular hypertrophy; ϕϕϕmorning fasting serum prolactin >18.77 ng/ml (males) and >24.20 ng/ml (females); ±neutrophils <1.5 x 103 cells/mm³ (moderate neutropenia), neutrophils <0.5 x 103 cells/mm³ (severe neutropenia); ±±serum sodium <136 mmol/L; ±±±serum potassium 3.0-3.5 mEq/L (mild hypokalemia); ±±±±serum magnesium <2.0 mg/dL; ¶clinically assessed signs and symptoms.