Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: the multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial

Anne Katrine Pagsberg, Pia Jeppesen, Dea Gowers Klauber, Karsten Gjessing Jensen, Ditte Rudå, Marie Stentebjerg-Olesen, Peter Jantzen, Simone Rasmussen, Eva Ann-Sofie Saldeen, Maj-Britt Glenn Lauritsen, Niels Bilenberg, Anne Dorte Stenstrøm, Louise Nyvang, Sarah Madsen, Thomas M Werge, Theis Lange, Christian Gluud, Maria Skoog, Per Winkel, Jens Richardt M Jepsen, Birgitte Fagerlund, Christoph U Correll, Anders Fink-Jensen

Summary

Background Head-to-head trials to guide antipsychotic treatment choices for paediatric psychosis are urgently needed because extrapolations from adult studies might not be implementable. In this superiority trial with two-sided significance testing, we aimed to compare the efficacy and safety of quetiapine-extended release (quetiapine-ER) versus aripiprazole in children and adolescents with first-episode psychosis, to determine whether differences between the two treatments were sufficient to guide clinicians in their choice of one drug over the other.

Methods In this multicentre, double-blind, randomised trial in seven Danish university clinics, we recruited children and adolescents aged 12–17 years with a diagnosis of ICD-10 schizophrenia-spectrum disorder, delusional disorder, or affective-spectrum psychotic disorder, and psychotic symptoms scoring at least 4 on at least one of the following Positive and Negative Syndrome Scale (PANSS) items: P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), and G9 (unusual thought content), and a total PANSS score greater than 60. Patients were randomly assigned (1:1) to 12 weeks of treatment with target doses of 600 mg/day of quetiapine-ER (starting from 50 mg/day) or 20 mg/day of aripiprazole (starting from 2·5 mg/day). The assigned drug was titrated over five levels, with 2 days at each dose, and the final dose achieved on day 9. Randomisation was done using a computer-generated concealed sequence with a block size of 8, and stratified by baseline PANSS positive score (≤20 points or >20 points) and age (12–14 years or 15–17 years). Study drugs were administered in identical capsules, and interventions, assessments, and data analysis were done masked. The primary outcome was PANSS positive score. Key adverse outcomes were bodyweight, homoeostatic model of insulin resistance (HOMA-IR), akathisia, and sedation. Analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01119014.

Findings Between June 10, 2010, and Jan 29, 2014, 231 participants were assessed for elegibility, of whom 113 were randomly assigned to quetiapine-ER (n=55) or aripiprazole (n=58). PANSS positive score did not differ between groups after 12 weeks (adjusted mean change –5·05 [5·46] for quetiapine-ER, –6·21 [5·42] for aripiprazole; p=0·98), but decreased over time in both groups (p<0·0001). Weight gain was more rapid with quetiapine-ER (p=0·0008), with an adjusted mean weight group difference at week 12 of 3·33 kg (SD 7·23; effect size 0·64; p<0·0001). The HOMA-IR group difference at week 12 favoured aripiprazole (adjusted mean log-transformed group difference 0·259 [SD 0·906]; effect size 0·35; p=0·0060). Akathisia was more common with aripiprazole at week 2 (observed in 34 [60%] of 57 patients; estimated 63·5%) than with quetiapine-ER (15 [30%] of 50; estimated 31·3%; p=0·0021), but not at other timepoints. Sedation proportions did not change significantly over time with either intervention (observed at weeks 2, 4, and 12, respectively, for quetiapine-ER in 43 [83%] of 52, 40 [83%] of 48, and 34 [72%] of 47 patients and for aripiprazole in 49 [89%] of 55, 52 [96%] of 54, and 44 [92%] of 48 patients), and the overall estimated probability combining all timepoints was significantly higher for aripiprazole (97·1%) than for quetiapine-ER (89·2%; p=0·012). In addition to sedation and akathisia, the most common adverse events were tremor (42 [79%] patients in the quetiapine-ER group *vs* 52 [91%] patients in the aripiprazole group), increased duration of sleep (47 [92%] *vs* 39 [71%]), orthostatic dizziness (42 [78%] *vs* 46 [81%]), depression (43 [80%] *vs* 44 [77%]), tension/inner unrest (37 [69%] *vs* 50 [88%]), failing memory (41 [76%] *vs* 44 [77%]), and weight gain (46 [87%] *vs* 38 [68%]).

Interpretation This first head-to-head comparison of quetiapine-ER versus aripiprazole in early-onset psychosis showed no significant group differences in severity of psychopathology after 12 weeks of treatment. Quetiapine-ER was associated with more metabolic adverse events and aripiprazole with more initial akathisia and, unexpectedly, more sedation. The limited antipsychotic efficacy and high level of adverse events were noticeable. This trial provides novel information for the treatment of early-onset psychosis and highlights the importance of adverse event profiles when choosing among antipsychotics for children and adolescents who often require chronic treatment.

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Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark, Glostrup, Denmark & Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (A K Pagsberg PhD, P Jeppesen PhD, D G Klauber MSc, K G Jensen PhD, D Rudå MD, S Rasmussen MD, M-B G Lauritsen MD, S Madsen MD, J R M Jepsen PhD); **Psychiatric Centre Copenhagen, Mental Health Services, Capital Region of Denmark, Copenhagen, Denmark & Laboratory of Neuropsychiatry, Department of Neuroscience and Pharmacology, University of Copenhagen, Copenhagen, Denmark** (M Stentebjerg-Olesen PhD, Prof A Fink-Jensen DMSc); **Psychiatric Centre Sct Hans, Mental Health Services, Capital Region of Denmark, Roskilde, Denmark & Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark** (P Jantzen MD); **Child and Adolescent Psychiatry, Regional In-Patient Care, Malmoe, Sweden** (E A-S Saldeen MD); **Child and Adolescent Psychiatry Research Unit, Region of Southern Denmark, Odense, Denmark & Faculty of Health Science, University of Southern Denmark, Odense, Denmark** (Prof N Bilenberg PhD, A D Stenstrøm PhD); **Mental Health Centre for Child and Adolescent Psychiatry, Region**

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Zealand, Roskilde, Denmark & Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (L Nyvang MD); Institute for Biological Psychiatry, Psychiatric Centre Sct Hans, Mental Health Services, Capital Region of Denmark, Roskilde, Denmark & Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (Prof T M Werge PhD); Department of Public Health, Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark (T Lange PhD); Center for Statistical Science, Peking University, Beijing, China (T Lange); Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark (C Gluud DMSc, M Skoog DMSc, P Winkel DMSc); Center for Neuropsychiatric Schizophrenia Research and Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Psychiatric Centre Glostrup, Capital Region of Denmark, Glostrup, Denmark & Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (J R M Jepsen, B Fagerlund PhD); Psychiatry Research, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY, USA (Prof C U Correll MD); Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, NY, USA (Prof C U Correll); and The Feinstein Institute for Medical Research, Manhasset, NY, USA (Prof C U Correll)

Correspondence to: Assoc Prof Anne Katrine Pagsberg, The TEA Trial Group, Research Unit, Child and Adolescent Mental Health Center, Mental Health Services, Capital Region of Denmark & Faculty of Health Science, University of Copenhagen, DK-2600 Glostrup, Denmark
anne.katrine.pagsberg@regionh.dk

See Online for appendix

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Introduction

Children and adolescents with psychosis have poorer outcomes and higher risk of treatment resistance and adverse effects compared with patients with adult-onset psychosis.[1] Second-generation antipsychotics are first-line treatments for early-onset schizophrenia, but drug choice is hindered by limited evidence from only 12 small, comparative, randomised clinical trials (listed in the appendix), and extrapolations from trials in adults and off-label use are common.[2,3] However, pharmacologically, children and adolescents are not small adults[4]—they deserve treatments that are based on age-specific evidence. Health authorities demand more research to protect minors from ineffective or unsafe treatments,[4] but this demand pertains only to placebo-controlled trials; however, clinicians have to decide between different active treatment choices, not between an antipsychotic versus placebo. Hence, the scarcity

Research in context

Evidence before this study

We searched PubMed from inception to March 1, 2010, with no language restrictions, for randomised clinical trials comparing an antipsychotic drug to one or more other antipsychotic drugs with participants aged below 18 years who were diagnosed with non-affective, non-organic psychosis or with mixed non-organic psychosis (affective or non-affective). Search terms can be found in the appendix. We excluded trials exclusively including patients with affective psychosis. We identified ten relevant trials published from 1984 to 2010, further adding one trial detected from the references of the retrieved studies that fulfilled our inclusion criteria, but that had included adolescents and young adults aged 16–28 years. The identified trials included very small samples, and, combined, they reported results from fewer than 300 patients. The trials covered the first-generation antipsychotics haloperidol, molindone, thiothixene, and thioridazine, and the second-generation antipsychotics clozapine, olanzapine, quetiapine, and risperidone. Overall, in line with findings in adults, these comparative studies showed equal efficacy among antipsychotic drugs in reduction of psychotic symptoms, with the exception of clozapine, which was superior to haloperidol and olanzapine in paediatric treatment-resistant schizophrenia. The adverse reaction profiles differed significantly between antipsychotic agents, but adverse effect differences seemed to be mostly similar to those found in adults.

Added value of this study

The TEA trial extends the evidence base regarding treatment of early-onset pyschosis in children and adolescents by reporting the first direct comparison of two of the most widely used antipsychotics, quetiapine and aripiprazole. Both drugs showed similar antipsychotic efficacy after 12 weeks. We found a possible advantage for quetiapine-ER on cognitive battery-measured global cognition and for aripiprazole on parentally scored executive functioning. Metabolic adverse reactions were more prominent with quetiapine extended release, whereas initial akathisia and, unexpectedly, sedation were more frequent with aripiprazole. For both drugs, sedation appears to affect most patients. Quetiapine might not be the drug of choice when cardiometabolic effects are a concern, whereas aripiprazole might be avoided in patients sensitive to neurological adverse reactions. The finding of residual illness in most patients and the high frequency of adverse effects are noteworthy.

Implications of all the available evidence

Antipsychotics are first-line treatment for psychosis in youth. Similarly to adults, selection of antipsychotic treatment for psychosis in children and adolescents depends primarily on the adverse reaction profile of the drug, because antipsychotics show comparable efficacy. Early-onset psychosis has a poorer prognosis than does adult-onset psychosis, and patients often need antipsychotic treatment for many years. The challenge of increased adverse effect sensitivity and a high likelihood of suboptimal treatment responses in the context of the limited evidence base and frequent off-label use indicates a strong need for more comparative treatment research. Although the evidence indicates that antipsychotic treatment for children and adolescents with psychosis is fairly safe, the need for further sufficiently powered trials of antipsychotic drugs is clear. Particularly, independently funded, active-controlled trials are needed and health authorities should consider whether registration trials comparing drugs with placebo should be mandated to include formal rating scales for adverse effects that are more comprehensive and sensitive than are spontaneously reported adverse effects. Finally, because monotherapy with an antipsychotic agent only insufficiently promotes response and remission, children and adolescents with psychosis and their families might be helped by effective adjunctive psychosocial treatments, but the evidence base is limited and further research is needed.

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of active controlled trials among antipsychotics in paediatric psychosis is particularly concerning. Moreover, independently funded randomised controlled trials in early-onset psychosis are very rare. In comparative studies, only clozapine has proven superiority among antipsychotics in both paediatric and adult treatment-resistant schizophrenia, but the risk of serious adverse reactions limits first-line use.[5]

Quetiapine is a low-affinity dopamine-D2 receptor antagonist with low propensity for extrapyramidal symptoms, but elevated risk of metabolic disturbances and sedation in youth.[6] Aripiprazole is a high-affinity dopamine-D2 receptor partial agonist with relatively low propensity for extrapyramidal symptoms, but akathisia is reported. Aripiprazole-induced weight gain and dyslipidaemia are modest, and hyperprolactinaemia and QT prolongation are uncommon.[7]

The objective of the Tolerability and Efficacy of Antipsychotics (TEA) trial was to compare the benefits and harms of quetiapine extended release (quetiapine-ER) versus aripiprazole for the treatment of early-onset psychosis. We chose these two antipsychotics because of their approval status for early-onset schizophrenia, the wide paediatric use globally and in Denmark,[3,8] their different receptor profiles, and the fact that no randomised controlled trial had yet compared these two drugs in children and adolescents with psychosis (appendix). In this superiority trial, we tested the hypothesis that differences in efficacy and tolerability between the two antipsychotics would be sufficiently large to guide clinicians in their choice of one antipsychotic over the other. Here we present data for 12 weeks of treatment. A separate, long-term effectiveness phase of the study (week 52 of follow-up) will be published separately.

Methods

Study design and participants

TEA is an investigator-initiated, independently funded, multicentre, double-blind, randomised trial. The TEA protocol has been published.[9]

We selected patients aged 12–17 years, who were inpatients or outpatients at seven child and adolescent mental health centres covering all Danish university clinics, with a diagnosis of ICD-10 schizophrenia-spectrum disorder, delusional disorder (F20, F22–25, F28–29), or affective-spectrum psychotic disorder (F30.2, F31.2, F31.5, F32.3, F33.3), verified with a semi-structured psychopathological interview using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (K-SADS-PL) 4 weeks after inclusion in the trial; a clinical indication for antipsychotic treatment; psychotic symptoms scoring at least 4 on at least one of the following Positive and Negative Syndrome Scale (PANSS)[10] items: P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), and G9 (unusual thought content), and a total PANSS score greater than 60; who were antipsychotic-naive or with limited exposure (defined as antipsychotic treatment for psychosis maximally within the past calendar year, or a maximum of 1 week total antipsychotic treatment for any non-psychotic disorder during their lifetime); and who could provide written informed carer consent.

We excluded patients who were undergoing compulsory treatment; had drug-induced or organic psychosis, severe somatic illness, or history of severe head trauma; were pregnant or lactating; had a diagnosis of substance dependence (ICD-10 F1X.2) within the last year; or an allergy towards the investigational drugs or lactose intolerance. Patients could also be excluded from the trial in case of substantial worsening of their clinical state during the trial (defined as increases of 20% or more from baseline on the PANSS total score).

To form a reference population for cognitive and somatic measures, we included a control sample of psychiatrically and somatically healthy youths from the Capital Region of Denmark who were recruited based on a random data extraction from the Danish Centralized Civil Register, a government-owned registry of all residents in Denmark (appendix). Controls were matched according to age, sex, and parental education as an indicator of socioeconomic status. Healthy controls did not receive any trial intervention.

The study was approved by the Ethics Committee of Capital Region Denmark: H-3-2009-123. Further approvals, methodological details, and full reference list of assessment instruments are available in the appendix.

For the **Danish Centralized Civil Register** see http://sundhedsdatastyrelsen.dk/da/forskerservice

Randomisation and masking

Patients were randomly assigned (1:1) to oral quetiapine-ER versus aripiprazole. The Copenhagen Trial Unit used a computer-generated allocation sequence with a block size of 8 that was unknown to the investigators for central randomisation, stratified by baseline PANSS positive score (≤20 points or >20 points) and age (12–14 years or 15–17 years). The corresponding randomisation code list was sent electronically to the data manager at Copenhagen Trial Unit. Interventions, assessments, and data analysis were done masked, with patients, investigators, and trial personnel all masked. The study drugs were administered in identical capsules. To ensure that patients from both groups received the same number of capsules at each level of the titration schedule, patients in the aripiprazole group received capsules containing an inactive preparation where necessary.

Procedures

The assigned drug was titrated over five levels, with 2 days at each dose, and the final dose achieved on day 9. For quetiapine-ER, the starting dose was 50 mg/day, increasing to 100, 200, 400, and finally 600 mg/day; for aripiprazole, the starting dose was 2·5 mg/day, increasing to 5, 10, 15, and finally 20 mg/day. Identical capsules

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were administered orally once daily in the evening. If clinically indicated, titration and dosing were adjusted (dose ranges: quetiapine-ER 50–800 mg/day; aripiprazole 2·5–30 mg/day). Concomitant medications were allowed, except for other antipsychotics.

Medical doctors, experienced in child and adolescent psychiatry, were trained and certified to conduct the diagnostic evaluation with the K-SADS-PL, including group rating sessions of videotaped interviews. In addition to regular group ratings, ad-hoc supervision was available throughout the trial from an experienced senior consultant (AKP) in child and adolescent psychiatry. PANSS training of all assessors was done by a professor in psychiatry (AF-J), who has been trained and certified at the PANSS Institute. During the 43-month inclusion period, 14 of 38 2-h PANSS group sessions were used for reliability assessments, with the remaining used for supervision. Reliability assessments were based on ratings from assessor pairs scoring taped videos.

For more on the **PANSS Institute** see http://www.panss.org

We assessed patients at baseline, week 2, week 4, and week 12, and assessed healthy controls at baseline and week 12 after inclusion. Psychopathology, adverse events, and clinical somatic status were assessed at all timepoints, whereas cognitive assessments were done only at baseline and week 12, and laboratory tests only at baseline, week 4, and week 12. Healthy controls had the same assessments as patients at baseline and week 12, except that controls had K-SADS-PL at baseline, did not have detailed assessment of suicidal ideation at week 12, and were only assessed with part of the PANSS (item N5 difficulties in abstract thinking).

Outcomes

The primary outcome was the PANSS positive subscale score. The key secondary outcomes were bodyweight, homoeostatic model assessment of insulin resistance (HOMA-IR), akathisia (Barnes Akathisia Rating Scale [BARS]), and sedation (Udvalg for Kliniske Undersøgelser [UKU] side-effect rating scale; appendix).

For psychopathology, exploratory outcomes were PANSS negative, PANSS general, PANSS total, and PANSS depressive subscales; Clinical Global Impressions—Severity and Improvement (CGI-S/I); Global Assessment of Psychosocial Disability (GAPD); response (defined as a PANSS total reduction ≥30% and a CGI-I score of 1 [very much improved] or 2 [much improved]); remission (defined as PANSS score ≤3 [mild] on all of the following items: delusions, conceptual disorganisation, hallucinations behaviour, blunted affect, social withdrawal, lack of spontaneity, mannerism/posturing, unusual thoughts); and suicidal ideation (K-SADS-PL suicidality items sum-score). For cognition or cognitive daily functioning, exploratory outcomes were neurocognitive performance tested with Brief Assessment of Cognition in Schizophrenia (BACS); interview-based assessment of cognition with Schizophrenia Cognition Rating Scale, Danish version (SCoRS-DK); and parental assessment of executive functioning with the Behavioural Rating Inventory of Executive Functions (BRIEF) questionnaire. For adverse events we used the UKU rating scale; Abnormal Involuntary Movement Scale (AIMS); Simpson Angus Scale (SAS); QT-interval prolongation; standard clinical laboratory tests; and use of anti-extrapyramidal-symptoms drugs. We recorded all-cause and specific-cause study discontinuation.

Assessors of all outcomes were medical doctors or nurses (only medical doctors assessed adverse effects) with clinical training in child and adolescent psychiatry and trained in the use of the assessment instruments by specialists (AKP, AFJ) in psychiatry and child and adolescent psychiatry.

We classified all events according to the UKU scale categories of psychiatric, neurological, autonomous, or other. The investigators then classified the adverse events for seriousness, causality, and expectedness, using best clinical judgment and knowledge of known adverse events for the investigated medical compounds (appendix).

Statistical analysis

The statistical analysis plan is available in the appendix. Based on a SD of 5·7 points on the mean PANSS positive score, a power of 80%, an α of 0·05, and a minimal clinically relevant difference of 3 PANSS positive scale points, we calculated that we required 112 participants.[9] We tested if the null hypothesis could be rejected for the primary and each of the key adverse outcomes. The first alternative hypothesis was that there would be a difference on the PANSS positive score between quetiapine-ER and aripiprazole after 12 weeks of treatment of at least 3 points and that quetiapine-ER would be associated with increased sedation, weight gain, and metabolic adverse effects whereas aripiprazole would be associated with increased akathisia.

The analyses were by intention to treat with two-sided tests. All analyses were adjusted by stratification variables (PANSS positive score and age), centre (centres from the University of Copenhagen were combined into one group, and remaining centres into another), and baseline value of the respective outcome when relevant and available. Missing data were handled by multiple imputations (appendix). For analysis of longitudinal data, we used a mixed model with repeated measures for continuous outcomes. For binary outcomes, we used a generalised linear mixed model (proc glimmix). The prespecified regression analysis focused on the effect of the two antipsychotics after randomisation using data collected at weeks 2, 4, and 12. All models initially included the time and an interaction term between time and intervention. If the interaction between time and intervention was insignificant, this term was removed from the model. If following this removal the main effect of time was also insignificant, time was removed from the model, leaving only the main effect of the intervention in the model. We present the results for the continuous

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outcomes as the difference between the adjusted estimated means at week 12, and calculated effect sizes on the basis of these results. Regarding akathisia, we supplemented with a χ^2 comparison of observed values to identify at which timepoint the two groups separated significantly.

We analysed and interpreted the primary outcome with a significance value of $p<0·05$. For the key adverse outcomes, $p<0·01$ was interpreted as significant, and p values from 0·01 to 0·05 were discussed. This approach was chosen as an alternative to applying correction for multiplicity. We did exploratory analyses of remaining outcomes with $p<0·05$ for hypothesis-generating purposes only. For the primary outcome, we investigated possible interactions between the intervention and the following a-priori defined patient subgroups: (1) schizophrenia-spectrum psychosis and (2) at least moderate illness severity (baseline PANSS total-score ≥80) to allow for comparisons with other early-onset psychosis trials, and (3) antipsychotic-naive (post-hoc defined) to evaluate the possible effect of prior antipsychotic use.

We based analyses of cognitive outcomes on *Z* scores, standardised according to a matched, healthy control group (appendix). Changes in BACS composite *Z* scores and BRIEF total *Z* scores from week 0 to week 12 were defined as changes in the treatment groups minus the average change in the healthy control group. We analysed the SCoRS global rating *Z* scores as simple changes.

We used R (version 3.3.1) for analysis of cognitive outcomes; SPSS (version 22) for descriptive statistics, intraclass correlation coefficients, and χ^2 comparisons of detailed surveillance of adverse events; and SAS (version 9.3) for all other analyses. This study is registered with ClinicalTrials.gov, number NCT01119014.

Role of the funding source

The funders of the trial had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 10, 2010, and Jan 29, 2014, 231 patients were assessed for eligibility, of whom 118 were screen failures. 113 participants were randomly assigned to

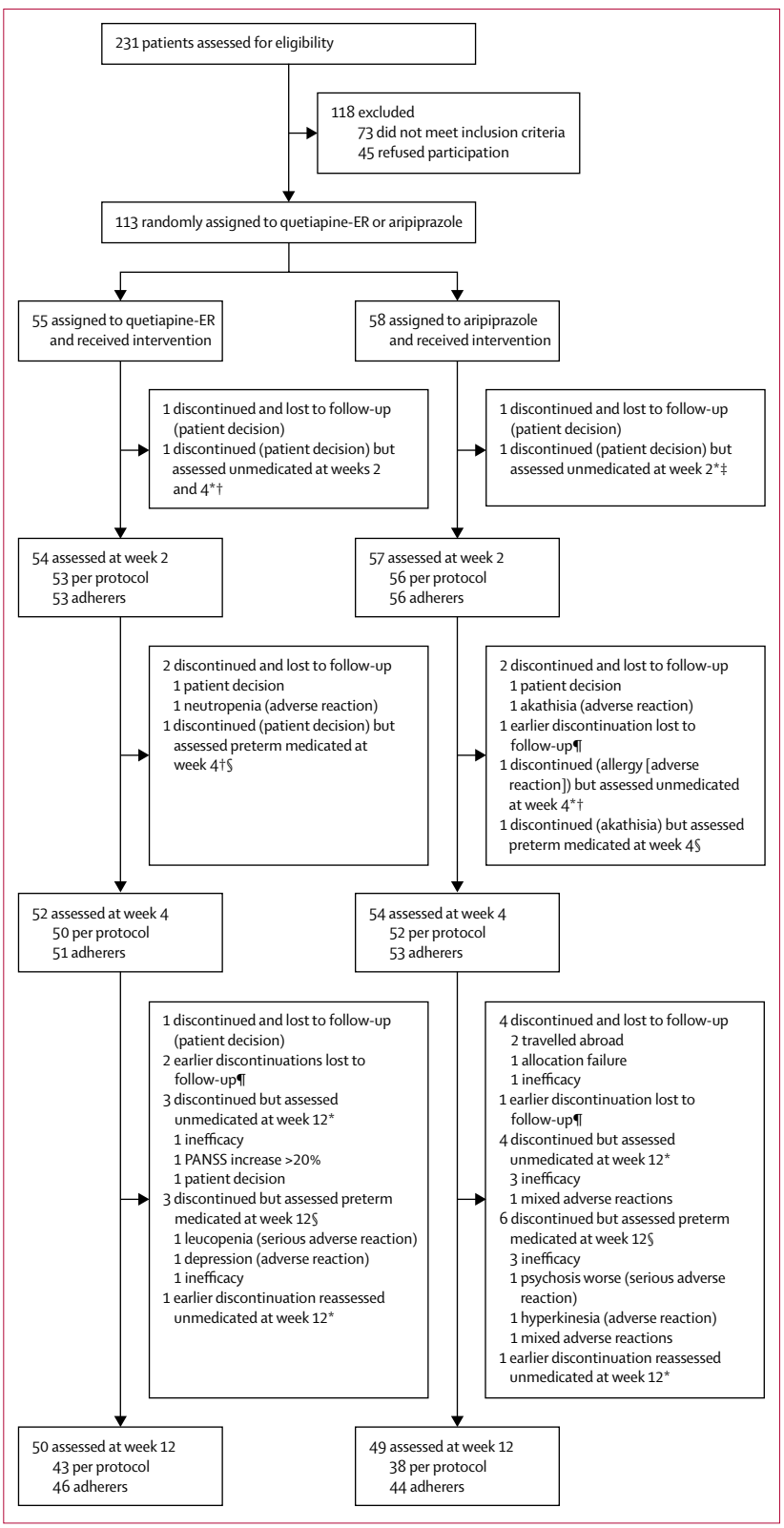

Figure 1: **Trial profile**

Patients assessed at each timepoint include those assessed unmedicated or preterm. Per protocol indicates number of participants assessed while medicated and on time. Adherers indicates number of participants assessed while medicated, but some preterm according to the planned date for assessment. PANSS=Positive and Negative Syndrome Scale. *Assessed at stated timepoints, but not included in adherers or per protocol. †Patient lost to follow-up at week 12. ‡Patient lost to follow-up at weeks 4 and 12. §Assessed at stated timepoints, but not included in per protocol. ¶Patients who had discontinued at an earlier timepoint but had been assessed unmedicated or preterm medicated.

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	Quetiapine-ER (n=55)	Aripiprazole (n=58)
Demographics		
Age (years; range 12–17)	15·8 (1·4)	15·7 (1·3)
Female	38 (69%)	41 (71%)
Male	17 (31%)	17 (29%)
Tanner stage,* males/females (range 1–5)	4·1 (1·0)/4·2 (0·7)	4·2 (0·8)/4·2 (0·6)
Illness		
ICD-10 diagnoses†		
F20: schizophrenia	33 (60%)	42 (72%)
F22: delusional disorders	2 (4%)	0
F23: acute and transient psychotic disorders	0	1 (2%)
F25: schizoaffective disorders	14 (25%)	9 (16%)
F28: other non-organic psychotic disorders	2 (4%)	2 (3%)
F31: bipolar disorders	0	1 (2%)
F32: depressive episode, psychotic	4 (7%)	3 (5%)
Psychopathology		
PANSS positive score (scale range 7–49)	19·9 (3·3)	20·6 (3·7)
PANSS negative score (scale range 7–49)	20·6 (5·4)	20·6 (5·3)
PANSS general score (scale range 16–112)	36·7 (5·9)	37·4 (7·0)
PANSS depression score (scale range 3–21)	10·5 (2·6)	11·0 (2·4)
PANSS total score (scale range 30–210)	77·2 (11·1)	78·6 (13·6)
CGI-S subscale score (scale range 1–7)	4·9 (0·8)	4·8 (0·6)
GAPD scale score (scale range 0–8)	4·5 (1·1)	4·3 (1·1)
Age at onset of psychotic symptoms (years)‡	13·2 (3·2)	13·0 (2·9)
(Continued from previous column)		
Treatment		
Antipsychotic-naive before inclusion	28 (51%)	29 (50%)
Prior antipsychotic treatment	27 (49%)	29 (50%)
Number of days of any prior antipsychotic	7 (1–16)	7 (1–12)
Aripiprazole	1 (2%)	2 (3%)
Median cumulated lifetime dose (mg)	15·00 (··)	27·50 (20–35)
Median number of days	6·0 (··)	7·5 (7–8)
Quetiapine	4 (7%)	5 (9%)
Median cumulated lifetime dose (mg)	138·00 (13–535)	675·00 (150–1250)
Median number of days	8·0 (1–23)	25·0 (3–27)
Olanzapine	12 (22%)	11 (19%)
Median cumulated lifetime dose (mg)	50·00 (18–243)	20·00 (10–110)
Median number of days	13·0 (1–25)	6·0 (1–11)
Chlorprothixene	20 (36%)	18 (31%)
Median cumulated lifetime dose (mg)	58·00 (20–195)	98·00 (40–160)
Median number of days	2·5 (1–9)	6·0 (1–8)
Concomitant non-antipsychotic psychotropics at baseline		
Melatonin	6 (11%)	14 (24%)
Antidepressants	9 (16%)	6 (10%)
Anxiolytics (benzodiazepines)	2 (4%)	1 (2%)
Mood stabilisers (eg, lamotrigine)	1 (2%)	0
Stimulants (eg, methylphenidate)	1 (2%)	0
Antihistamines (eg, phenergan for sedation)	1 (2%)	0

Data are n (%), mean (SD), or median (IQR). Recruitment distribution among regional centres: Capital Region, n=91 (started recruitment 2010); Region of Southern Denmark, n=10 (2011); Region Zealand, n=9 (2012); Central Denmark Region, n=1 (2013); North Denmark Region, n=2 (2010). ICD-10=International Classification of Disorders, version 10 (WHO). PANSS=Positive and Negative Syndrome Scale. CGI-S=Clinical Global Impression—Severity. GAPD=Global Assessment of Psychosocial Disability. PANSS depression score=sum scores on item G2 (anxiety), G3 (guilt feelings) and G6 (depression). *Tanner stages of pubertal maturation scale goes from 1 (pre-pubertal) to 5 (adult). †Diagnoses as per the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL). ‡n=109. Three cases of missing data and one outlier removed from analysis of time for first onset of psychotic symptoms.

Table 1: **Baseline demographic, illness, and treatment characteristics**

quetiapine-ER (n=55) or aripiprazole (n=58; figure 1). Screen failures did not differ significantly from randomised patients regarding mean age (p=0·57) or sex distribution (p=0·21). All randomised participants received at least one dose of the assigned treatment and were included in the intention-to-treat analyses. Overall, 12 (22%) of 55 patients in the quetiapine-ER group versus 20 (35%) of 58 patients in the aripiprazole group discontinued the trial medication before week 12 (p=0·14). Mean time to all-cause discontinuation was 72·6 days (SD 22·6) with quetiapine-ER versus 64·9 days (26·3) with aripiprazole (p=0·12; appendix).

Participants had first-episode psychosis, primarily within the schizophrenia/delusional disorder spectrum (table 1). Psychopathological severity was moderate to marked, and participants were seriously psychosocially disabled. Both groups seemed balanced in baseline proportions of participants using antidepressants, anxiolytics, mood stabilisers, or antihistamines, but more participants were treated with melatonin in the aripiprazole group than in the quetiapine-ER group (table 1).

Mean modal doses in the trial were 451·82 mg/day (SD 198·92) for quetiapine-ER and 14·61 mg/day (6·87) for aripiprazole—both were 75% of the target doses. Mean doses during the entire 12 weeks of study period

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were 426·39 mg/day (169·25) for quetiapine-ER and 12·97 mg/day (5·46) for aripiprazole, and mean maximum doses were 550·91 mg/day (185·74) for quetiapine-ER and 18·66 mg/day (6·16) for aripiprazole. Altogether, eight (15%) patients on quetiapine-ER versus eight (14%) patients on aripiprazole received no co-medications (p=0·91). Antipsychotic co-medication (protocol deviation due to rescue intervention) happened in 19 (35%) patients in the quetiapine-ER group versus 22 (38%) patients in the aripiprazole group (p=0·49). We found no significant differences in use of other co-medications, except for more anti-extrapyramidal-symptoms drugs with aripiprazole (14 [24%]) versus quetiapine-ER (four [7%]; p=0·014; appendix).

Proportion of missing values ranged from 7·5% to 16·5%. We identified auxiliary variables for all continuous outcomes, prompting multiple imputations; this was not the case for binary outcomes. For PANSS positive scores, we used 30 imputations to make the inferences sufficiently precise. Otherwise, we used 10 imputations.

The observed mean PANSS positive scores at baseline and week 12 changed from 19·9 (SD 3·3) to 15·0 (4·6) for quetiapine-ER and from 20·6 (3·7) to 14·4 (5·1) for aripiprazole (adjusted mean change –5·05 [5·46] for quetiapine-ER, –6·21 [5·42] for aripiprazole; table 2). PANSS positive scores declined over time in both groups (p<0·0001) without significant main differential effects (table 3). At week 12, the between-group difference in mean estimated PANSS positive score adjusted for centre, stratification variables, and baseline values was –0·0085 points (SD 5·93; effect-size –0·002; p=0·89). For PANSS positive scores, we found no significant interaction between the intervention and any of the three subgroups: (1) patients diagnosed with schizophrenia (n=75): regression coefficient –0·622 (SD 13·6), p=0·64; (2) patients with baseline PANSS total scores of 80 or more (n=44): regression coefficient 1·161 (12·9), p=0·38; and (3) patients with prior antipsychotic exposure (n=56): regression coefficient –0·934 (12·5), p=0·44. Figure 2 shows the observed scores for all PANSS measures. Intraclass correlation coefficients (ICCs) for nine rating sessions (from the pair of assessors with the highest common number of ratings) were PANSS positive 0·91 (95% CI 0·59–0·98), PANSS negative 0·93 (0·57–0·98), PANSS general 0·96 (0·80–0·99), and PANSS total 0·91 (0·61–0·98). ICCs for two to six sessions (the remaining pairs of assessors) ranged as follows: PANSS positive 0·67–0·77, PANSS negative 0·46–0·99, PANSS general 0·64–0·79, and PANSS total 0·60–0·94 (appendix).

Observed mean bodyweight increased for both groups (table 2). We found a significant effect of time on bodyweight in both groups, with a differential main effect of the intervention and a significant interaction between time and intervention—ie, bodyweight increased more rapidly with quetiapine-ER (table 3). At week 12, the group difference in mean adjusted estimated weight was 3·33 kg (SD 7·23; effect size 0·64; p<0·0001).

The observed HOMA-IR changed from 3·10 (SD 0·42) at baseline to 4·32 (0·67) at week 12 for quetiapine-ER and from 2·92 (0·54) to 2·74 (0·20) for aripiprazole. HOMA-IR showed a significant main differential effect of the intervention, favouring aripiprazole, without a significant effect of time (table 3). At week 12, the group difference in mean adjusted estimated log HOMA-IR was 0·259 (0·906; effect size 0·35; p=0·0060).

Akathisia was significantly more likely with aripiprazole than with quetiapine-ER, without significant change over time in both groups (table 3; appendix). However, the p value of the interaction between time and intervention was close to 0·01. Therefore, we retained the time effects in the model when testing the main effect of the intervention (table 3). Based on χ^2 comparison of observed values, the difference in akathisia was significant at week 2 (p=0·0021), but not at week 4 (p=0·1160) or week 12 (p=0·6056).

	Week 0	Week 2	Week 4	Week 12
PANSS positive score				
Quetiapine-ER				
Observed	19·9 (3·3); n=55	16·8 (3·5); n=51	16·2 (3·8); n=50	15·0 (4·6); n=49
Imputed	..	16·8 (3·6)	16·2 (4·0)	14·9 (5·1)
Imputed, adjusted	..	..	..	14·1 (6·2)
Aripiprazole				
Observed	20·6 (3·7); n=58	17·8 (4·0); n=56	16·2 (4·5); n=54	14·4 (5·1); n=47
Imputed	..	17·9 (4·0)	16·2 (4·6)	14·4 (5·7)
Imputed, adjusted	..	..	..	14·1 (6·0)
Bodyweight (kg)				
Quetiapine-ER				
Observed	63·2 (13·8); n=55	65·5 (14·1); n=52	66·6 (14·3); n=50	69·6 (15·9); n=46
Imputed	..	64·6 (14·6)	65·5 (14·6)	68·2 (16·2)
Imputed, adjusted	..	..	..	67·4 (5·3)
Aripiprazole				
Observed	61·3 (10·7);n=58	61·4 (10·7); n=54	61·8 (10·7); n=54	63·1 (11·8); n=49
Imputed	..	61·6 (10·7)	61·7 (10·5)	62·9 (11·8)
Imputed, adjusted	..	..	..	64·0 (5·2)
Log HOMA-IR†				
Quetiapine-ER				
Observed	0·863 (0·748); n=50	..	1·178 (0·683); n=46	1·213 (0·642); n=43
Imputed	0·839(0·760)	..	1·160 (0·673)	1·217 (0·703)
Imputed, adjusted	..	..	..	1·139 (0·760)
Aripiprazole				
Observed	0·770 (0·686); n=49	..	0·844 (0·485); n=50	0·895 (0·479); n=45
Imputed	0·750 (0·670)	..	0·839 (0·535)	0·957 (0·598)
Imputed, adjusted	..	..	..	0·880 (0·732)

(Table 2 continues on next page)

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	Week 0	Week 2	Week 4	Week 12
(Continued from previous page)				
Akathisia‡				
Quetiapine-ER				
Observed	..	15 (30%); n=50	16 (32%); n=50	15 (32%); n=47
Estimated from model	..	31·3% (8·1)	31·6% (8·8)	33·0% (9·8)
Aripiprazole				
Observed	..	34 (60%); n=57	25 (47%); n=53	13 (27%); n=48
Estimated from model	..	63·5% (9·0)	55·3% (8·8)	24·1% (9·8)
Sedation§				
Quetiapine-ER				
Observed	..	43 (83%); n=52	40 (83%); n=48	34 (72%); n=47
Estimated from model	..	89·2% (4·9)	89·2% (4·9)	89·2% (4·9)
Aripiprazole				
Observed	..	49 (89%); n=55	52 (96%); n=54	44 (92%); n=48
Estimated from model	..	97·1% (1·8)	97·1% (1·8)	97·1% (1·8)

Data are mean (SD) or number of patients affected (%). For estimated coefficients of the regression analyses, see table 3. The number of evaluable patients (n) for each observed outcome is given for each timepoint. For continuous variables, means of the multiply imputed data are also shown for comparison with the observed data, which had varying percentages of missing values and were multiply imputed because auxiliary variables were identified. Imputed and estimated data are based on the original group sizes (n=55 for quetiapine-ER and n=58 for aripiprazole). Baseline frequencies for sedation are not included, due to control for baseline status intrinsic in UKU evaluation at follow-up—ie, at every assessment the investigator evaluates whether the event is probably related to any of the study drugs, including an evaluation of change since baseline UKU. HOMA-IR=Homoeostatic model of insulin resistance. BARS=Barnes Akathisia Rating Scale. UKU=Udvalg for Kliniske Undersøgelser rating scale. †For HOMA-IR—calculated by {[fasting plasma glucose (mmol/L)*fasting plasma insulin (pmol/L)/6·0]/22·5}—week 2 values are not available because laboratory tests were available only at baseline, week 4, and 12. Multiple imputation was done using log-transformed values. Exponential of the difference between the means of the log-transformed values shows the ratio between the back transformed means. ‡Akathisia defined as a score of at least 2 (mild) on the global item of BARS. Baseline values are not included due to the definition in psychopharmacological context of akathisia as related to dopamine blockade of a drug. §Sedation defined as a UKU rating scale score of at least 1 (mild) on item 1.2 (asthenia/lassitude/increased fatiguability) AND rated possible or probable on "related to study drug" OR a score of at least 1 (mild) on item 1.3 (sleepiness/sedation) AND rated possible or probable on "related to study drug".

***Table 2*: Observed and estimated values of the primary outcome (PANSS positive score) and the four key adverse outcomes during 12 weeks of intervention**

	Intervention	Time	Time*intervention interaction
PANSS positive score	0·012 (6·03), p=0·98	−0·270 (0·40), p<0·0001	Not significant (p=0·076)
Bodyweight (kg)	0·605 (2·70); p=0·042	0·133 (0·347); p=0·0081	0·227 (0·560); p=0·0008
Log HOMA-IR*	0·257 (1·29; SD 0·880); p=0·0060	Not significant (p=0·23)	Not significant (p=0·65)
Akathisia†	1·70 (7·65); p=0·0023	0·0081 (0·660); p=0·87	−0·179 (0·960); p=0·011
Sedation (UKU)‡	1·39 (7·60); p=0·012	Not significant (p=0·11)	Not significant (p=0·18)

Data are estimated regression coefficients (SD). Adjustments were made for centre, protocol-specified stratification variables, and—for PANSS positive, weight, and HOMA-IR—the baseline variable. For HOMA-IR and sedation, only the main effect of the intervention was left in the model, implying that the mean values over time are constant. HOMA-IR=Homoeostatic model of insulin resistance. BARS=Barnes Akathisia Rating Scale. UKU=Udvalg for Kliniske Undersøgelser. *Log-transformed values are used in the regression analysis (exponential value of the difference between the means of the log-transformed values show the back transformed means). †Akathisia defined as a score of at least 2 (mild) on the global item of BARS. Baseline values are not included due to the definition in psychopharmacological context of akathisia as related to dopamine blockade of a drug. ‡Sedation defined as a UKU rating scale score of at least 1 (mild) on item 1.2 (asthenia/lassitude/increased fatiguability) AND rated possible or probable on "related to study drug" OR a score of at least 1 (mild) on item 1.3 (sleepiness/sedation) AND rated possible or probable on "related to study drug".

***Table 3*: Estimated coefficients of the regression analysis**

For sedation (covering increased fatiguability [UKU item 1.2] and sedation [UKU item 1.3]), the main differential effect of the intervention was borderline significant according to our predefined thresholds for the key adverse outcomes (p<0·01), being more common with aripiprazole than with quetiapine-ER. Because we found no significant effects of time, data for all three timepoints were combined to obtain an overall estimate of the probability of sedation in the two groups (table 2, table 3). For comparative reasons, we analysed post hoc the two UKU items included in sedation separately and found converging results (appendix).

We explored the interaction between the intervention and each stratification variable and centre; all values were p>0·1.

The observed data of additional outcomes and results of the adjusted analyses are shown in the appendix. The following comparisons were significant (p<0·05). At week 12, the least-squares-estimated (lsmean) sum scores on SAS (measuring extrapyramidal symptoms) were larger with aripiprazole (lsmean 2·74) than with quetiapine-ER (1·31; mean difference −1·433, 95% CI −2·014 to −0·851; p<0·0001), whereas the natural logarithm of body-mass index was larger with quetiapine-ER (lsmean 3·14 [exp(3·14)=23·0]) than with aripiprazole (3·09 [exp(3·09)=21·9]; ratio 1·05, 95% CI 1·03 to 1·07; p<0·0001). At week 12, mean plasma levels adjusted for baseline values of triglycerides, cholesterol, low-density lipoprotein, and prolactin were all higher with quetiapine-ER versus aripiprazole (for prolactin, this result indicates a larger decrease with aripiprazole compared with quetiapine, due to the calculation method). We found no group differences at week 12 on PANSS subscales, CGI scales, GAPD scale, and suicidality scores.

On BACS composite *Z* scores, the quetiapine-ER group showed an increase in cognitive performance over time comparable to that of healthy controls and significantly better than that of the aripiprazole group, which showed decreased performance over time (estimate 0·65 [SE 0·15], p<0·0001). Post-hoc analyses found significant differences only in verbal fluency and symbol coding, with favourable change scores in the quetiapine-ER group compared with the aripiprazole group (verbal fluency: estimate 0·41 [SE 0·12], p=0·001; symbol coding: estimate 0·85 [0·15], p<0·0001). Parental assessments of executive functions (BRIEF total *Z* score) showed increased performance in executive functions over time in the aripiprazole group and a more favourable development than in the quetiapine-ER group in which the performance on executive functions decreased (estimate 1·42 [0·42], p=0·0007). The interview-based assessment of cognition (SCoRS global rating) showed no difference in cognitive change scores between quetiapine-ER and aripiprazole (estimate 0·36 [0·47], p=0·44; appendix).

The mean count of neurological adverse reactions per person was higher with aripiprazole than with quetiapine-ER (table 4), and more patients in the aripiprazole group

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had at least one neurological adverse reaction than did patients in the quetiapine-ER group (table 4). The mean count of autonomic adverse reactions was also higher with aripiprazole than with quetiapine-ER (table 4). Numbers of serious adverse events and reactions were similar between groups (table 4). No suspected unexpected serious adverse reactions occurred.

At week 12, 24 (44%) patients in the quetiapine-ER group had gained at least 7% in weight compared with nine (16%) in the aripiprazole group (adjusted logistic regression: relative risk [RR] 3·01, 95% CI 1·62–4·47, p=0·001; reference aripiprazole group). The response rate was 11 (23%) of 48 patients with quetiapine-ER compared with 11 (23%) of 47 patients with aripiprazole (RR 0·98, 95% CI 0·42–1·90; p=0·96). Remission had occurred by week 12 in ten (20%) of 49 patients with quetiapine-ER compared with 11 (23%) of 47 patients with aripiprazole (RR 0·85, 95% CI 0·36–1·69; p=0·67). One patient in the aripiprazole group and no patients in the quetiapine group developed dyskinesia (a score ≥2 on any AIMS-subscale during weeks 0–12).

No clinically significant changes in vital signs, standard laboratory tests (appendix), or electrocardiograms (besides those of the serious adverse events or reactions; table 4) were observed in either group. Some group differences were found (or confirmed) for the detailed surveillance of harms (appendix) according to the UKU rating scale. A higher frequency (ie, p<0·05) of the following adverse events was observed with quetiapine-ER compared with aripiprazole: concentration difficulties (38 [72%] of 53 *vs* 32 [56%] of 57), increased duration of sleep (47 [92%] of 51 *vs* 39 [71%] of 55), emotional indifference (38 [70%] of 54 *vs* 28 [49%] of 57), reduced salivation (additional reports; eight [15%] of 55 *vs* one [2%] of 58), weight gain (at least 1 kg in the past month or since start of the trial; 46 [87%] of 53 *vs* 38 [68%] of 56), nose bleeding (eight [15%] of 55 *vs* two [3%] of 58), increased metabolic laboratory measures (additional reports; five [9%] of 55 *vs* 0), and infections (additional reports; 23 [42%] of 55 *vs* 14 [24%] of 58). A higher frequency of the following adverse events was observed with aripiprazole compared with quetiapine-ER: tension/inner unrest (50 [88%] of 57 *vs* 37 [69%] of 54), reduced duration of sleep (24 [42%] of 57 *vs* six [11%] of 53), rigidity (22 [39%] of 57 *vs* two [4%] of 53), hypokinesia (22 [39%] of 57 *vs* seven [13%] of 53), akathisia (47 [83%] of 57 *vs* 32 [59%] of 54), accommodation disturbances (32 [56%] of 57 *vs* 15 [28%] of 54), increased salivation (32 [56%] of 57 *vs* six [11%] of 54), nausea/vomiting (34 [60%] of 57 *vs* 22 [41%] of 54), photosensitivity (24 [42%] of 57 *vs* 11 [21%] of 52), and weight loss (at least 1 kg in the past month or since the start of the trial; 22 [39%] of 56 *vs* five [9%] of 53).

Overall, the detailed surveillance of harms found 31 adverse events affecting more than 20% of the sample. Of those, ten symptoms affected more than 70% of the sample (fatiguability, sedation, failing memory, depression, tension/inner unrest, increased duration of sleep, tremor, akathisia, orthostatic dizziness, and weight gain; appendix). In addition to sedation and akathisia, the most common of these were tremor (42 [79%] patients in the quetiapine-ER group *vs* 52 [91%] patients in the aripiprazole group), increased duration of sleep (47 [92 %] *vs* 39 [71%]), orthostatic dizziness (42 [78%] *vs* 46 [81%]), depression (43 [80%] *vs* 44 [77%]), tension/inner unrest (37 [69%] *vs* 50 [88%]), failing memory (41 [76%] *vs* 44 [77%]), and weight gain (46 [87%] *vs* 38 [68%]).

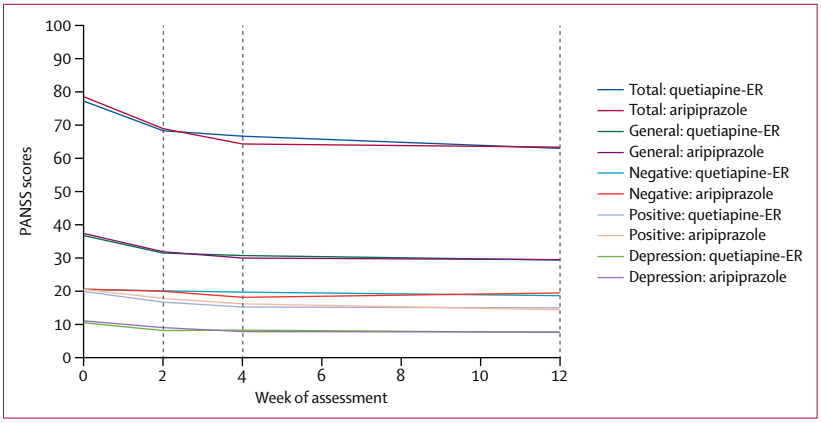

Figure 2: **Change over time in observed mean PANSS total and subscores assessed at weeks 0 (baseline), 2, 4, and 12**
PANSS=Positive and Negative Syndrome Scale.

Discussion

In this multicentre, randomised, double-blind trial of children and adolescents with first-episode psychosis (mainly schizophrenia), we found no significant group difference on mean PANSS positive score at week 12 between quetiapine-ER and aripiprazole. Mean weight gain and HOMA-IR were higher with quetiapine-ER than with aripiprazole, whereas sedation and initial akathisia were more frequent with aripiprazole than with quetiapine-ER. With aripiprazole, more patients required drugs for treatment of extrapyramidal symptoms. Response, remission, frequency of trial discontinuation, and time to all-cause discontinuation were similar between groups.

Based on our sample size estimation, we have the power to conclude (with a 20% risk of missing a true difference) that no clinically significant group difference existed on the PANSS positive score at week 12. Previous comparative trials, using smaller samples, showed significant PANSS positive score reductions for individual drugs in the range of 6–9 points (25–35% from baseline values around 25), and insignificant group differences among antipsychotics in the range of 0·5–4 points.[11–13] The placebo-controlled quetiapine registration trial[14] in youths showed a significant mean PANSS positive score change difference between quetiapine and placebo of approximately 3 points, and the parallel CGI improvement was of 2·45 points (ie, much-to-minimally improved) in the quetiapine

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	Count data*			Number and percentage affected		
	Quetiapine-ER	Aripiprazole	p value†	Quetiapine-ER	Aripiprazole	p value‡
Adverse event						
Psychiatric	309, 5·64 (5·17), 0–18	307, 5·31 (5·20), 0–23	0·76	43 (78%)	45 (78%)	0·94
Neurological	52, 0·95 (1·51), 0–6	40, 0·69 (1·27), 0–5	0·27	22 (40%)	17 (29%)	0·23
Autonomic	117, 2·13 (3·18), 0–16	123, 2·12 (2·11), 0–9	0·25	31 (56%)	42 (72%)	0·08
Other	143, 2·60 (2·48), 0–11	147, 2·53 (2·70), 0–11	0·60	44 (80%)	45 (78%)	0·10
All categories	621, 11·3 (9·08), 0–43	617, 10·7 (8·59), 0–38	0·84	51 (93%)	55 (95%)	0·71
Adverse reaction						
Psychiatric	633, 11·5 (6·99), 0–30	717, 12·4 (4·88), 0–23	0·25	52 (95%)	57 (98%)	0·36
Neurological	216, 3·93 (3·01), 0–12	351, 6·05 (2·96), 0–12	0·0002	48 (87%)	57 (98%)	0·03
Autonomic	340, 6·18 (4·21), 0–17	470, 8·10 (4·77), 0–22	0·027	52 (95%)	55 (95%)	1·00
Other	236, 4·29 (2·85), 0–13	232, 4·00 (3·05), 0–12	0·65	52 (95%)	48 (83%)	0·05
All categories	1425, 25·9 (12·8), 0–61	1770, 30·5 (11·6), 0–54	0·021	54 (98%)	57 (98%)	1·00
Serious adverse event						
Psychiatric	2 (aggravation of psychosis), 0·036 (0·19), 0–1	2 (aggravation of psychosis), 0·034 (0·19), 0–1	0·96	2 (4%)	2 (3%)	1·00
Neurological	0	0	1·00	0	0	..
Autonomic	1 (stomachache/nausea), 0·018 (0·13), 0–1	1 (heart rhythm disorder), 0·017 (0·13), 0–1	0·98	1 (2%)	1 (2%)	1·00
Other	1 (appendicitis), 0·018 (0·13), 0–1	0	0·32	1 (2%)	0	0·49
All categories	4, 0·035 (0·26), 0–1	3, 0·052 (0·22), 0–1	0·65	4 (7%)	3 (5%)	0·71
Serious adverse reaction						
Psychiatric	8 (4 suicidality; 4 aggravation of psychosis plus suicidality), 0·15 (0·45), 0–2	10 (3 suicidality, 3 aggravation of psychosis, 3 aggravation of psychosis plus suicidiality, 1 depression), 0·19 (0·61), 0–3	0·85	6 (11%)	7 (12%)	0·85
Neurological	1 (severe extrapyramidal symptoms), 0·018 (0·13), 0–1	0	0·32	1 (2%)	0	0·49
Autonomic	1 (cardiac symptoms), 0·018 (0·19), 0–1	0	0·32	1 (2%)	0	0·49
Other	1 (leucocytopenia), 0·018 (0·13), 0–1	0	0·32	1 (2%)	0	0·49
All categories	11, 0·20 (0·49), 0–2	10, 0·19 (0·61), 0–3	0·54	9 (16%)	7 (12%)	0·51

UKU=Udvalg for Kliniske Undersøgelser rating scale. *Count data are total number, mean number of events per person (SD), range. †Non-parametric test used (Mann-Whitney). ‡χ^2 or Fisher's exact test used as appropriate.

Table 4: **Comparisons between quetiapine-ER and aripiprazole of the distributions of adverse events or reactions graded according to seriousness and UKU clinical category**

800 mg/day arm, and 3·22 (minimally improved to no change) in the placebo arm. We predetermined that a minimal clinically relevant group difference of 3 points on PANSS positive score at week 12 would provide a relevant basis for choosing between drugs—ie, large enough to discriminate true clinical differences, and aiming at a moderate effect size around 0·5.[9] Our mean estimated adjusted PANSS positive score group difference at week 12 was close to zero, and the effect size was negligible.

The inclusion of broadly defined psychosis in our study mirrors clinical practice, thereby enhancing external validity, but hinders direct comparisons with other trials, which primarily investigated patients with strictly defined schizophrenia or schizophrenia-spectrum disorders. The antipsychotic naivety (50% of patients) or very limited pre-exposure (median 1 week) to antipsychotics in the other half of the sample reduced the risk of confounding of the results by drug order and carry-over effects; however, there was no washout period before randomisation. Yet, we found no significant interactions between the intervention and any of three relevant subgroups (patients with schizophrenia, PANSS total score ≥80, or prior antipsychotic exposure) regarding the main outcome.

The low proportion of male participants (30%) differs from similar studies in early-onset psychosis that had a male proportion of around 60–70%.[15] However, a Danish study[16] using a nationwide population-based mental health register showed a decreasing male–female ratio for early-onset schizophrenia in the period 1971–2010, with a male proportion of 40% in 2010. Most trials of antipsychotics in early-onset schizophrenia reported mean baseline PANSS positive scores of around 25 and mean PANSS total scores of 90–100,[17] but our sample had a more modest baseline illness severity (PANSS positive 20, PANSS total 77), which might partly explain the overall limited symptom reduction, because higher baseline illness severity predicts greater antipsychotic treatment response.[18] Moderate baseline symptom severity might indicate early detection; however, the average time from onset of psychotic symptoms to the treatment of the first psychotic episode, which coincided with referral to TEA, was approximately 30 months

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(median duration of untreated psychosis 16 months). This period is longer than the duration of untreated psychosis found in a recent review[15] of 35 studies of paediatric schizophrenia-spectrum psychosis (mean 17·2 months [SD 12·8]), but within the range of means (2–45 months) for the reviewed studies[15] and converging with an average duration of untreated psychosis of 32 months for participants aged 15–18 years in the Canadian Prevention and Early Intervention Psychoses Program.[19]

The mean modal doses in TEA were 75% of the target doses for both compounds. Because dosing was flexible and could be adjusted according to the individual clinical treatment response, the fact that the average doses used were in the middle of the ranges permitted suggests that patients were probably neither under-dosed nor overdosed. The option of regulating the dose during the trial flexibly provided us with data that can guide future dosing in children and adolescents with first-episode psychosis who generally require lower doses than do chronically ill patients. In the placebo-controlled, 6-week registration trial[14] in adolescents with schizophrenia, quetiapine 400 mg/day showed mean PANSS positive score reduction of 8·56 (SE 0·737) and 800 mg/day showed a reduction of 9·34 (0·587), and no major differences in adverse reactions. A similar pattern in another registration trial[20] in adolescents with schizophrenia was seen for aripiprazole 10 mg/day (mean PANSS positive score change –7·6 points [SE 0·6]) and 30 mg/day (–9·1 points [0·6]). The only other randomised controlled trial[21] we found that investigated one of our study drugs in adolescents with schizophrenia compared paliperidone with aripiprazole in a flexible dose design over 26 weeks. In that study, the mean dose of aripiprazole was 11·56 mg/day (SD 3·00), range 5–15 mg/day, which was close to the mean dose used in our trial.

We found no significant differences between quetiapine-ER and aripiprazole on psychopathology and psychosocial functioning. Our results are similar to those seen in studies with adults,[22,23] although one trial[24] indicated less efficacy for quetiapine than for aripiprazole in first-episode non-affective psychosis. A network meta-analysis[25] on the acute treatment of schizophrenia-spectrum disorders in 2158 children and adolescents aged 8–19 years showed comparable efficacy among six (aripiprazole, quetiapine, paliperidone, risperidone, olanzapine, molindone) of eight antipsychotics (efficacy inferior for ziprasidone and unclear for asenapine). Specifically, no significant difference was found on PANSS positive reduction when indirectly comparing aripiprazole with quetiapine (standard mean difference 0·32, 95% CI –0·13 to 0·77).

The adverse event profiles found in TEA are generally consistent with the literature.[1] The network meta-analysis[25] found less severe and fewer adverse events for aripiprazole and quetiapine than for antipsychotics with similar efficacy. However, even though the pattern of adverse events in TEA is consistent with the meta-analytic findings, the numbers of adverse events and serious adverse events in TEA are much higher than in the meta-analysis, in which those numbers were at placebo level. For instance, sedation frequencies in TEA were 97% for aripiprazole and 89% for quetiapine-ER, which is higher than reported in trials[14,20,21,26] investigating aripiprazole or quetiapine that were included in the meta-analysis (10–30%). In TEA, aripiprazole was significantly more sedative than quetiapine, which was not found in the network meta-analysis and contrasts with findings in adults in whom quetiapine had a moderate and aripiprazole a low risk for somnolence.[27] A trial[11] by Arango and colleagues investigating quetiapine in a broader spectrum of adolescents with first-episode psychosis found a sedation rate of 79%. The similarity with the TEA result might be explained by the use of rating scale-based assessments of sedation (UKU) in both trials. Other trials used rating scales only for neuromotor adverse effects, and details on other harms were collected from unsolicited self-reporting.

The higher use of melatonin in the aripiprazole versus the quetiapine-ER group at baseline (table 1) was followed by a more even exposure during the trial. Reduced duration of sleep according to UKU was more prominent with aripiprazole than quetiapine-ER, which might in part explain daytime sedation. However, this finding does not explain the higher frequency of sedation with aripiprazole in TEA compared with other studies, which—in addition to the rating scale-based capturing of adverse effects—could be due to the large proportion of antipsychotic-naive participants.

The limited beneficial effects in the context of the observed level of adverse events in the TEA trial are noteworthy. Without a placebo group, our trial cannot demonstrate any effects that might be ascribed to the antipsychotics. Nevertheless, the significant main effect of time on the reduction of psychotic symptoms supports the assumption that both medications have a beneficial effect in early-onset psychosis, which is consistent with evidence from placebo-controlled trials[14,20] of both antipsychotics in adolescent schizophrenia.

Proportion of patients achieving response in antipsychotic trials in paediatric schizophrenia range from 30% to 78% for the active drug (quetiapine-ER 30–38%; aripiprazole 53–71%) and from 26% to 54% for placebo.[25] Our finding of low response rates (23%) for both aripiprazole and quetiapine-ER might partly be explained by less strict definitions of response in other trials (≥30% PANSS total reduction, without demanding CGI improvement;[14,20] ≥20% PANSS total score reduction and CGI improvement score of 1 or 2[13]). However, even after 12 weeks, the PANSS positive score reductions in TEA (5–6 points) were lower than those in the 6-week, placebo-controlled trials (quetiapine 9 points; aripiprazole 8 points).[14,20] In those trials, patients underwent a washout

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or cross-tapering period, and baseline PANSS total scores were generally in the high 90s (minimum 80)—almost 20 points higher than in TEA—providing more room for improvement. The discrepancy between response rates in TEA and the primarily industry-sponsored trials indicates that despite high design quality of these trials, blinding might be hampered, especially in placebo-controlled trials of drugs with distinct adverse event profiles. Rating on different scales requires judgments by the assessor involving the perception of, for instance, patient symptom severity, which can be influenced by bias. Clinicians might be poorly blinded when confronted with signs of adverse events that indicate patients belong to the active trial arm.

As many as 98% of patients in the total sample experienced adverse reactions. In comparison, the placebo-controlled pediatric quetiapine trial[14] showed an overall proportion of adverse reactions of only 46–56% (no available information on the aripiprazole trial[20]). This discrepancy might be due to our active surveillance of harms and that our investigators were potentially better blinded.

The cognitive results point to different treatment effects favouring quetiapine-ER over aripiprazole on objectively measurable global cognitive functioning (BACS), perhaps particularly driven by increased performance over time in fluency and speed of information processing. This result is consistent with findings from a meta-analysis[28] of studies of adults with schizophrenia that found quetiapine to have a better effect on attention and processing speed than did other tested compounds (albeit not including aripiprazole). The results on changes in subjective parental assessment of executive functions (BRIEF) showed superiority of aripiprazole over quetiapine-ER, which was associated with a decrease in executive functions. The interview-based, subjective assessment of cognition (SCoRS) did not indicate a difference in change in cognition between treatment groups. Supposing that sedation might affect cognitive measures, the results appear to partly contradict our findings of more sedation with aripiprazole than with quetiapine-ER. However, nearly all patients, regardless of investigational drug, had sedation complaints. Although the aripiprazole group displayed the highest proportion of sedation, the group still increased cognitive performance on BACS from week 0 to week 12 (albeit to a lesser degree than in the quetiapine-ER group) and the aripiprazole group reduced the executive problems on BRIEF from the week 0 rating to the week 12 rating (which the quetiapine-ER group did not). Taken together, we found no apparent association between sedation and change in cognitive performance or executive problems.

Assessment for inter-rater reliability of more instruments than PANSS and more PANSS sessions would have strengthened our results. However, we aimed to ensure valid and reliable results by exclusively employing assessors who were medical doctors and nurses experienced in clinical child and adolescent psychiatry. These raters were specifically trained in use of validated instruments, group ratings of K-SADS-PL and PANSS took place regularly, and supervision from consultants engaged in the trial was available at all times.

The TEA trial extends the evidence base for antipsychotic choice in the treatment of psychosis in youth, suggesting that clinicians should primarily base antipsychotic choice between quetiapine and aripiprazole on adverse reactions, as beneficial effect differences were undiscernible or, regarding cognition, showed mixed results. Quetiapine might not be the drug of choice when cardiometabolic effects are a concern, whereas aripiprazole might be avoided in patients sensitive to neurological adverse reactions, although our data indicate that akathisia might primarily be a temporary problem, as described in adults.[29] The high proportion of adverse reactions seen with both antipsychotics emphasises that rigorous adverse event assessments are crucial in the management of early-onset psychosis. The level of adverse reactions might increase the challenge of continuing antipsychotic treatment in early-onset psychosis, which is well described in the TEOSS trial[30] in which only 12% of youths with early-onset schizophrenia spectrum disorders continued on their originally randomised treatment at 52 weeks.

The somewhat limited beneficial but notable adverse effects reported for both antipsychotics here raise the questions whether independently funded placebo-controlled trials are needed and whether registration trials should be mandated to include formal rating scales not only for efficacy, but also for safety.

Contributors

AKP takes responsibility for the integrity of the work as a whole, from inception to publication. AKP, PJe, DGK, KGJ, DR, MS-O, CG, JRMJ, BF, CUC, and AF-J designed the trial. AKP, DGK, KGJ, DR, MS-O, PJa, SR, EA-SS, M-BGL, NB, ADS, LN, and SM recruited the participants. AKP, DGK, KGJ, DR, MSO, SR, EA-SS, M-BGL, NB, ADS, LN, SM, and JRMJ assessed the participants. AKP, PJe, PJa, EA-SS, and M-BGL implemented the trial in the Capital Region; SR, LN, and SM implemented the trial in the Zealand Region; and NB and ADS implemented the trial in the Southern Region. PW, AKP, CG, and AF-J designed the statistical analysis plan, which was written by PW. DR, DGK, AKP, and the Copenhagen Trial Unit cleaned the data. PW analysed the data, supplemented by AKP. TL analysed the cognitive data based on a statistical analysis plan outlined by AKP and JRJ and detailed by TL. AKP drafted the paper, assisted by PW, AF-J, CC, JRMJ, BF, and CG. All authors critically revised the paper and approved the final draft.

Declaration of interests

TMW has acted as a lecturer and consultant to H Lundbeck A/S. SR has participated in an ADHD congress, sponsored by HB Pharma. ADS has received honoraria from Otsuka. CUC has received grants or research support from the Bendheim Foundation, National Institute of Mental Health, Patient Centered Outcomes Research Institute, Takeda, and the Thrasher Foundation. He has served as a consultant to Alkermes, Forum, the Gerson Lehrman Group, IntraCellular Therapies, Janssen/Johnson and Johnson, Lundbeck, MedAvante, Medscape, Otsuka, Pfizer, ProPhase, Sunovion, and Takeda. He has presented expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He has served as a member of the Data Safety Monitoring

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Boards for Lundbeck, and Pfizer. AF-J has conducted an independent investigator-initiated and University-initiated study supported by an unrestricted grant from Novo Nordisk. TL sits on a Data Safety Monitoring Board for Novo Nordisk. The remaining authors declare no competing interests.

Acknowledgments

Primary Investigators: Marlene Briciet Lauritsen (Aalborg University Hospital, Psychiatry and Clinical Institute, Aalborg, Denmark), Per Hove Thomsen (Department of Child and Adolescent Psychiatry, Aarhus University Hospital, Risskov, Denmark).
Advisory board: Kerstin Jessica Plessen (Child and Adolescent Mental Health Centre, Capital Region Mental Health Services, Copenhagen, Denmark), Hans-Christoph Steinhausen (Department of Child and Adolescent Psychiatry, University Hospital of Psychiatry Zurich, Zurich, Switzerland; Clinical Psychology and Epidemiology, Department of Psychology, University of Basel, Basel, Switzerland; Child and Adolescent Mental Health Centre, Capital Region Mental Health Services, Copenhagen, Denmark).
Good Clinical Practice Units: Kristina Devantier (GCP unit at Copenhagen University Hospital, Copenhagen, Denmark), Christina Pihl Truelsen (GCP unit at Copenhagen University Hospital, Copenhagen, Denmark), Louise Berendt (formerly GCP unit at Copenhagen University Hospital, Copenhagen, Denmark, now Novo Nordisk A/S, Søborg, Denmark), Lene Brandsborg (GCP unit at Aalborg and Aarhus University Hospitals; Aarhus, Copenhagen), Charlotte Calov (GCP unit at Odense University Hospital, Odense, Denmark).
Data Monitoring and Safety Board: Lars Vedel Kessing (Psychiatric Center Copenhagen, Copenhagen University Hospitals, Copenhagen, Denmark), Jesper Brok (Cancer Section, University College London, Institute of Child Health, UK; Department of Paediatric Haematology and Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; Great Ormond Street Hospital, London, UK).
Nurses: Louise Hedegaard (Child and Adolescent Mental Health Centre, Capital Region Mental Health Services, Copenhagen, Denmark), Sanne Rosenfeldt Fald Hansen (Department of Child and Adolescent Psychiatry, University of Southern Denmark, Odense, Denmark), Sinne Fenger Eybye (Psychiatric Center Stolpegaard, Capital Region Mental Health Services, Copenhagen, Denmark), Sofie Eldon (Psychiatric Center Ballerup, Capital Region Psychiatry, Copenhagen, Denmark), Ann Hornum (Center for Autism, Nørresundby; Denmark).
Investigators: Rebekka Gudmundsson Perlick (Child- and adolescent psychiatric unit, Psychiatric Center Torshavn, Torshavn, Faroe Islands), Natasa Stajic (Psychiatric Center Copenhagen, Capital Region Mental Health Services,Copenhagen, Denmark), Ditte Lammers Vernal (Aalborg University Hospital, Psychiatry, Aalborg, Denmark).
Medical students: Natasha Askbo (Psychiatric Center Ballerup, Capital Region Mental Health Services, Copenhagen, Denmark), Sarah Gørtz (General Practice Medical Center of Ganløse, Ganløse, Denmark), Anne Sofie Schott Andersen (Child and Adolescent Mental Health Centre, Capital Region Mental Health Services, Copenhagen, Denmark), Sabrina Krøigaard (Psychiatric Center Vordingborg, Region Zealand University Hospital, Vordingborg, Denmark).
Trial preparations: Torben Sørensen Carlsen (Clinic for Children and Adolescents, Copenhagen, Denmark), Jimmi Nielsen (Psychiatric Center Glostrup, Capital Region Psychiatry, Copenhagen, Denmark), Rikke Hilker (Psychiatric Center Glostrup, Capital Region Mental Health Services, Copenhagen, Denmark), Dorthe Baunbjerg Nielsen (Herlev Hospital, Centre of Cancer Research, Capital Region, Herlev, Denmark), Anne Marie Råberg Christensen (Child and Adolescent Mental Health Centre, Capital Region Mental Health Services, Copenhagen, Denmark).
Academic secretariat: Louise Munkholm (Department of Social Sciences and Business, Roskilde University, Roskilde, Denmark), Karin Frydenlund Jespersen (Herlev Hospital, Capital Region, Herlev, Denmark), Mette Justesen (formerly Child and Adolescent Mental Health Centre, Capital Region Psychiatry, Copenhagen, Denmark, now Novo Nordisk, Bagsværd, Denmark), Bente Berg (Statistics Denmark, Copenhagen, Denmark), Tania Storm (Shelter Pegasus, Copenhagen, Denmark), Arendse Bohr (Kgs. Lyngby, Denmark), Nana Suldrup Jørgensen (Copenhagen, Denmark).
Laboratory staff at participating centres: Merete Frejstrup Pedersen (Nordsjællands University Hospital, Hillerød, Denmark), Liselotte Pflug (Glostrup University Hospital, Glostrup, Denmark), Ingelise Marcusssen (Bispebjerg University Hospital, Copenhagen, Denmark). Further, we thank Alice Rosendahl and Yvonne Neergard (Capital Region Pharmacy, Copenhagen, Denmark); Lisbeth Nymark Jørgensen and Gerda Demant Olesen (Research Institute for Biological Psychiatry, Roskilde, Denmark); Jane Lindschou and Ema Erkocevic Petersen (Copenhagen Trial Unit, Copenhagen, Denmark); and all clinical and administrative staffs at the participating child and adolescent psychiatry departments. We thank Christina Hedegård Bruhn, Specialist Adviser, (Pharmacovigilance and medical devices, Danish Medicines Agency, Copenhagen, Denmark) for help with figures concerning the use of antipsychotics in youth in Denmark. A total of DKK 18 703 207 (£2 102 949) was funded by the following public and private funds: The National Research Council for Health and Disease Foundation for Health Promotion (DKK 293 722); AP Møller Foundation (DKK 50 000); Rosalie Petersens Foundation (DKK 60 000); Stevn and Rindom Foundation (DKK 50 000); Foundation for the Promotion of Medical Science (DKK 66 000, 50 000); The Capital Region Psychiatric Research Foundation (DKK 1 530 000, 880 000, 2 475 000, 67 000, 120 000, 1 521 667); Tryg Foundation (DKK 5 558 703); Region of Southern Denmark Research Foundation (DKK 1 410 900); Danish Psychiatric Research Educational Fund (DKK 150 000); Psychiatry Foundation (DKK 1 000 000); Foundation of 17-12-1981 (DKK 600 000); Psychiatric Research Foundation Region Zealand (DKK 100 000, 250 000); Capital Region Strategic Research Foundation (DKK 800 000); Knud og Dagny Andresens Foundation (DKK 100 000); Psychiatric Research Foundation of 1967 (DKK 40 000); The Capital Region Research Foundation (DKK 180 000); Dr Sofus Carl Emil Friis and Hustru Olga Friis Scholarship (DKK 722 215); Tømrerhandler Johannes Fogs Foundation (DKK 25 000); Brdr Hartmanns Foundation (DKK 150 000); Aase and Ejnar Danielsens Foundation (DKK 100 000); Jacob Madsen and wife Olga Madsens Foundation (DKK 10 000); CC Klestrup and wife Scholarship (DKK 20 000); Lundbeck Foundation Scholarship (DKK 140 000); and Tømrermester Jørgen Holm and wife Elisas Scholarship (DKK 183 000).

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