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Effect of aripiprazole as an adjunct to atypical antipsychotics on weight and metabolic profile: a 12-week open-label trial

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Abstract

Background: Atypical antipsychotics are widely prescribed, yet have been associated with weight gain and metabolic syndrome.

Aim: To study the effect of adjunct low-dose aripiprazole on weight and metabolic parameters of subjects on atypical antipsychotics (olanzapine, clozapine or risperidone).

Methods: The study was carried out as an open-label trial with a fixed dose of 5 mg aripiprazole added to the patient's current antipsychotic for 12 weeks. The primary outcome measure was mean change in weight, while secondary outcome measures included change in waist circumference; fasting blood glucose; HbA1c; triglycerides; total, HDL and LDL cholesterol levels; functioning; and neurocognition.

Results: For the overall study ($n = 55$), there was no significant effect of adjunct aripiprazole on the weight of the subjects. However, the clozapine group achieved significant weight loss ($p = 0.002$) and also had significant improvements in total cholesterol ($p < 0.001$), HDL ($p = 0.016$), LDL ($p = 0.044$) and triglyceride levels ($p = 0.038$). The olanzapine group had significant improvement in triglycerides ($p = 0.001$), and other metabolic parameters for this group showed improvement trends, but did not reach statistical significance. The risperidone group did not show any significant improvement in weight or metabolic parameters.

Conclusions: The study adds support to the adjunctive use of aripiprazole to clozapine for weight loss and improvement in metabolic profile, and for reduction in cardiometabolic risk for patients on olanzapine.

Trial Registration: Clinicaltrials.gov identifier: NCT02949752

Keywords: aripiprazole, weight gain, metabolic syndrome, atypical antipsychotics

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Introduction

Schizophrenia is a chronic neuropsychiatric illness, and long-term antipsychotic medications are the mainstay of treatment.[1] The first generation of antipsychotics, commonly referred to as typical antipsychotics, targeted mainly dopamine D2 receptors and led to disabling extrapyramidal side effects.[2] The antipsychotics introduced later, referred to as second generation or atypical antipsychotics (SGAs), acted on a wider range of receptors.[3] The SGAs had lower propensity for extrapyramidal side effects at clinically effective doses and showed improved efficacy on negative, cognitive and affective symptoms.[4–6] Thus, the SGAs found quick acceptance and their usage increased rapidly, such that they are now the more commonly prescribed drugs in large parts of the world.[7–11] The distinction between atypical and typical antipsychotics has since been called into question as many atypicals behave like typicals, and a new classification among atypicals has been proposed, introducing the concept of spectrum of

atypia that begins with risperidone (the least atypical) and ends with olanzapine and clozapine (the most atypical).[12]

Patients with schizophrenia are at risk of developing metabolic syndrome (MetS), with the prevalence of MetS being 1.5-fold higher than that of the general population.[13,14] The MetS is a well-described cluster of interrelated risk factors for developing cardiovascular disease and type 2 diabetes. The main components of MetS are elevated waist circumference, hypertension, hyperglycaemia and dyslipidaemia.[15] The MetS is associated with a 2-fold increase in cardiovascular mortality and a 1.5-fold increase in all-cause mortality,[16] and individuals with MetS are five times more likely to develop type 2 diabetes.[17]

The use of SGAs was associated with reports of dramatic weight gain, diabetes [including diabetic ketoacidosis (DKA)] and an atherogenic lipid profile [increased low-density lipoprotein (LDL) cholesterol and triglyceride levels and decreased high-density lipoprotein (HDL) cholesterol], such that the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists and the North American Association for the Study of Obesity convened a consensus development conference in 2003 on the subject.[18] The position statement from the conference concluded that there was considerable evidence, particularly in patients with schizophrenia, that treatment with SGAs can cause a rapid increase in body weight in the first few months of therapy that may not reach a plateau even after 1 year of treatment. Clozapine and olanzapine, which produced the greatest weight gain, were associated with the greatest increases in total cholesterol, LDL cholesterol, and triglycerides and with decreased HDL cholesterol. Since then, evidence of the link of SGAs with metabolic abnormalities has further accumulated.[3,19,20]

Several strategies have been tried to ameliorate the impact of SGAs on MetS, including dietary advice, physical exercise, counselling and enrolment in targeted health programmes.[21,22] In addition to these, pharmacological strategies such as antipsychotic switching and adjunctive use of medications have been investigated for countering the metabolic side effects.[23]

Studies have suggested aripiprazole as a potential candidate for switching strategies to improve metabolic parameters.[24–26] However, the rate of treatment discontinuation was higher in the aripiprazole group in the studies. Furthermore, clinicians are reluctant to switch antipsychotics solely to address metabolic side effects, particularly if the patient has achieved remission or clinically meaningful symptom reduction on their current antipsychotic.[27] In clinical practice, it is also challenging to switch when patients may have a belief of superior efficacy in their current antipsychotic.[24] Olanzapine and clozapine are two of the most effective antipsychotics, proven to have better efficacy than others.[5,28] Together with risperidone, they are also among the highest prescribed antipsychotics, despite clear concerns about their impact on weight and metabolic profile.[29,30]

Aripiprazole as an adjunct has also been investigated for improving metabolic profile; a multicentre, randomised, double-blind placebo-controlled trial studying the effect of adjunctive aripiprazole (dose range 5–15 mg; mean 11.1 mg) on body weight and clinical efficacy in patients on clozapine found significant weight loss and reduction in body mass index (BMI) and waist circumference in favour of aripiprazole, with no significant differences in symptom improvement or adverse events (AEs).[31] A randomised, double-blind placebo-controlled study to examine aripiprazole's effect on glucose metabolism in clozapine-treated patients with schizophrenia using the frequently sampled intravenous glucose tolerance test (a gold standard procedure to assess insulin sensitivity and the effectiveness of glucose metabolism) found that adjunctive aripiprazole treatment in clozapine-treated patients improved certain aspects of glucose metabolism including insulin sensitivity.[32] There are further studies that have explored adjunct aripiprazole with clozapine and olanzapine, with mostly positive findings.[33–35] As a result, use of aripiprazole as an adjunct has received cautious endorsement in reviews and clinical practice guidelines.[23,36–38]

In this study, we set about evaluating the effect of adjunct use of aripiprazole at a fixed dose of 5 mg on metabolic profile and weight in patients stabilised on atypical antipsychotics olanzapine, clozapine and risperidone. We hypothesised that aripiprazole, due to its pharmacological profile, can be used as an adjunct to atypical antipsychotics at a low dose to induce weight loss and improve metabolic profile with fewer side effects and greater clinical acceptability. The primary objective of the study was to assess mean change in

weight 12 weeks after the use of adjunct aripiprazole. The secondary end points included changes in the metabolic parameters (waist circumference; fasting blood glucose; HbA1c; total, HDL and LDL cholesterol levels; triglycerides).

Method

Study design

The study was an open-label, 12-week prospective study conducted between May 2016 and September 2019 at the outpatient clinic at the Institute of Mental Health (IMH), Singapore. IMH is the sole tertiary psychiatric hospital in Singapore that caters to over 40,000 patients annually at its outpatient clinic. Enrolled participants were prescribed a fixed dose of 5 mg aripiprazole per day, in addition to their antipsychotic. This dose was decided based on an audit of the local clinical practice that suggested that a 5-mg adjunct dose of aripiprazole had a good balance of efficacy and side effects and lower risk of discontinuation.[39] During the 12-week study, if for any reason there was a change in the dose of the primary antipsychotic or switch of the antipsychotic, the participant was then withdrawn from the study. Medication compliance was assessed by pill counts.

Safety and tolerability were measured by Simpson Angus Scale (SAS total score), Side Effects Checklist, Barnes Akathisia Scale (BAS), Abnormal Involuntary Movement Scale (AIMS), AEs or serious AE reports.

The study was carried out in accordance with the principles of Good Clinical Practice and the relevant local health regulations. Ethics approval was obtained from the National Healthcare Group's Domain Specific Review Board (Reference: 2016/00106). The study was registered at trial registry clinicaltrials.gov (Identifier: NCT02949752). Participants were required to provide written informed consent in English at the point of recruitment.

Subjects

The study recruited outpatients aged 21–65 years with a diagnosis of schizophrenia or schizoaffective disorder. The subjects were required to be on stable doses of atypical antipsychotics, olanzapine, clozapine, or risperidone, for at least 1 month. Antipsychotic polypharmacy was permitted, as long as there was only one of the above three atypical antipsychotics. At baseline, subjects were required to have a BMI $\geqslant$25 kg/m^2 (i.e. overweight and above) or $\geqslant$7% increase in weight from pre-antipsychotic treatment.

The study excluded subjects who had a previous allergy to aripiprazole or contraindication to the use of aripiprazole. Participants with current substance misuse or those non-adherent to current prescribed medications were excluded. It was required that subjects had no major or unstable medical or neurological illness (such as uncontrolled diabetes and hypertension) and were not using any medications for weight loss during the preceding month. Participants with serious suicidal thoughts or who posed a serious risk of harm to self or to others were excluded. The study did not recruit women who were pregnant or breastfeeding. Participants who had clinically significant abnormalities on enrolment examination and screening that required active intervention, that is, initiation of lipid lowering agent or antidiabetic medication, were also excluded.

Metabolic measurements

Weight, BMI and waist circumference were measured at baseline and at every subsequent visit (weeks 0, 4, 8 and 12). A fasting venous blood sample was collected from each participant at baseline and at the last visit (week 12). Serum level of total cholesterol, HDL, LDL, and triglycerides and glucose levels were obtained at an accredited laboratory that analysed the samples using Roche diagnostics C702 and C513 HbA1c analysers.

Assessment and end points

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS)[40] and the Clinical Global Impression–Severity and Improvement scales (CGI-I and CGI-S).[41] Functioning was assessed on the Global Assessment of Functioning Scale (GAF),[42] while World Health Organization Disability Assessment Scale (WHODAS 2.0)[43]was used to assess disability across various domains. All assessments were performed by trained raters who had achieved satisfactory inter-rater reliability [i.e. intraclass correlation coefficient (ICC) $>$0.8]. Neurocognition was assessed using the symbol coding and digit span tasks, components of the Brief Neurocognitive Assessment, which included

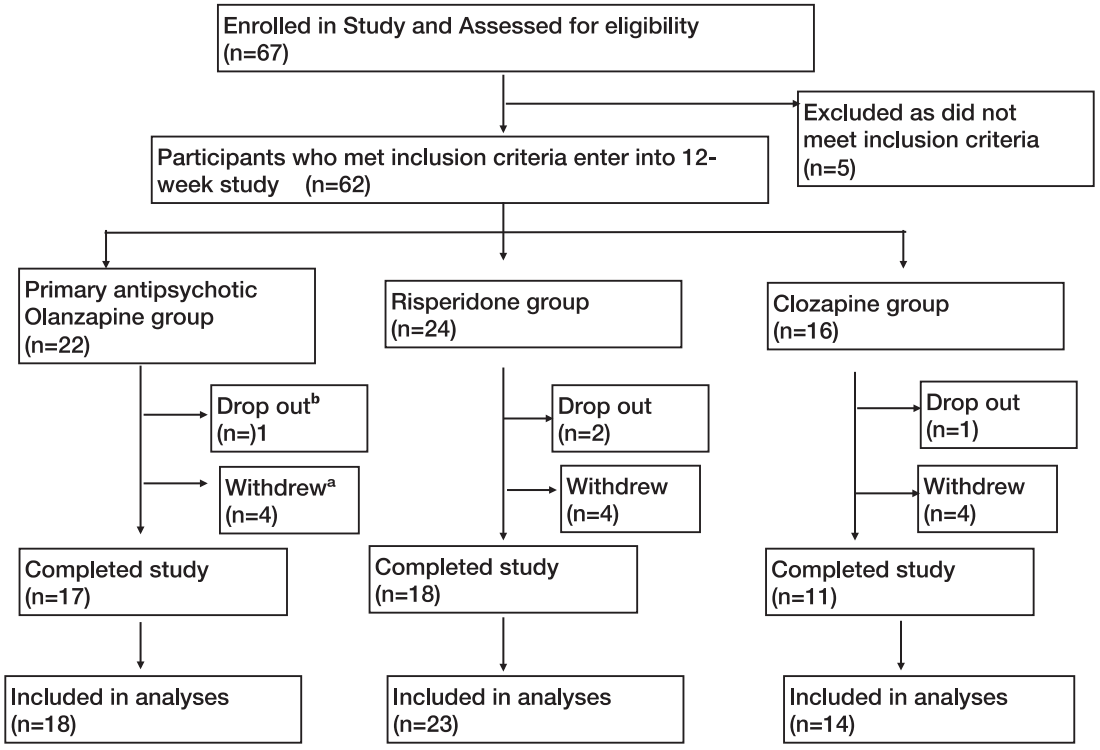


Figure 1. Patient flow diagram through the trial as per CONSORT guidelines.
[a]Subjects were withdrawn from the study for any of the following reasons: non-compliance ($n = 1$), abnormal baseline blood results/abnormalities in the results such that medication changes were required ($n = 4$), social issues ($n = 2$), patient/family's request ($n = 4$) and mental state deterioration ($n = 1$).
[b]Subjects dropped out from the study for any of the following reasons: loss to follow-up ($n = 1$) and side effects ($n = 3$).

working memory and processing speed cognitive domains.[44]

Safety and tolerability

Side effects were evaluated using the SAS, BAS, AIMS, Side Effects Checklist and AE reports.

Statistical analysis

All statistical analyses were performed using SPSS Version 22 (IBM) and SAS software. The primary outcome measure was the mean change in body weight from baseline to week 12 using last observation carried forward (LOCF) data. The sample size of 42 patients (14 in each antipsychotic arm) was designed to yield 80% power to detect a difference of 1.6 kg in the mean change from baseline in weight at week 12 (LOCF).[39] This calculation assumed a standard deviation of 2.3. Allowing for withdrawals, it was expected that 60 patients would need to be recruited. The mean changes were evaluated using generalised estimating equations model with baseline measurement, age, gender and chlorpromazine equivalent dose as covariates, and treatment group as main effects. A further analysis was carried for each individual antipsychotic group (olanzapine, clozapine and risperidone).

Results

A total of 67 individuals were screened for the study; 55 patients were included in the final analysis (including those who withdrew but attended for exit visit), of which 18 were on olanzapine, 23 were on risperidone and 14 were on clozapine (see Figure 1). The clinical and demographic details of the participants are shown in Table 1. The mean dose of olanzapine was 11.9 mg (SD = 5.7) (range: 5–20), of clozapine was 292.9 mg (SD = 115.8) (range: 125–500) and of risperidone was 3.2 mg (SD = 1.6)(range: 0.5–6).

Metabolic parameters

Thirty-one (56.4%) participants recorded weight loss after 12 weeks of adjunctive aripiprazole [13 (92.9%) out of 14 for clozapine, 8 (44.4%) out of 18 for olanzapine and 10 (43.5%) out of 23 for risperidone). Among the participants with documented

Table 1. Clinical and demographic characteristics of the study sample ($n = 55$).

	Overall sample *n* (%)	Olanzapine ($n = 18$) *n* (%)	Risperidone ($n = 23$) *n* (%)	Clozapine ($n = 14$) *n* (%)
Age, mean (SD)	39.3 (8.2)	37.7 (6.8)	43.8 (7.7)	33.9 (6.6)
Sex				
Female	27 (49.1)	7 (38.9)	12 (52.2)	8 (57.1)
Male	28 (50.9)	11 (61.1)	11 (47.8)	6 (42.9)
Ethnicity				
Chinese	39 (70.9)	13 (72.2)	13 (56.5)	13 (92.9)
Malay	11 (20.)	3 (16.7)	8 (34.8)	0 (0)
Indian	4 (7.3)	1 (5.6)	2 (8.7)	1 (7.1)
Others	1 (1.8)	1 (5.6)	0 (0)	0 (0)
Diagnosis				
Schizophrenia	46 (83.6)	13 (72.2)	19 (82.6)	14 (100)
Schizoaffective disorder	9 (16.4)	5 (27.8)	4 (17.4)	0 (0)
Medication groups				
Olanzapine	18 (32.7)	–	–	–
Risperidone	23 (41.8)	–	–	–
Clozapine	14 (25.5)	–	–	–
Dosage (mg/day), mean (SD)		11.9 (5.7) (range 5–20)	3.2 (1.6) (range: 0.5–6)	292.9 (115.8) (range: 125–500)

weight loss, the average weight loss was 1.82 kg (SD = 1.64). Overall, there was no significant change in weight, BMI or waist circumference between week 0 and week 12 (see Table 2).

In addition, there was significant reduction in total cholesterol ($\beta = -0.28$, $p = 0.001$), LDL ($\beta = -0.17$, $p = 0.038$) and triglycerides ($\beta = -0.47$, $p = 0.005$) in the overall study sample. An analysis of completers ($n = 46$) *versus* LOCF did not lead to a change in the findings.

Symptoms and functioning

There were statistically significant improvements in CGI-S ($\beta = -0.22$, $p = 0.017$) and GAF ($\beta = 5.04$, $p < 0.001$) scores from baseline to week 12; however, there were no significant difference in PANSS and WHODAS scores (Table 2).

Safety and tolerability

A total of 20 patients reported suffering from any kind of AE, with the most common being anxiety ($n = 4$), dizziness ($n = 3$), sedation ($n = 3$), constipation ($n = 3$), tachycardia ($n = 3$), restlessness ($n = 2$) and akathisia ($n = 2$) (see Table 3). After acceptance into the study and commencing the study medication, four subjects dropped out of the study: three due to side effects and one was lost to follow-up. Eight participants were withdrawn from the study: four due to patient/family request, two due to social issues (housing/work), one due to deterioration in mental state assessed to be unrelated to the study medication and one due to non-compliance. Mean total SAS, BAS and AIMS scores were very low at study entry with no significant increases at the end of the study. For AIMS, nine subjects (16.3%) had baseline scores >1 (median, 2; range, 1–5), while at visit 4, seven subjects (12.7%) had AIMS score >1 (median, 2; range, 1–3). For BAS, six

Table 2. Mean change in weight and other outcomes between baseline and 12-week follow-up in the overall sample ($n = 55$).

	Baseline		12-week		Paired *t* test		Generalised estimating equations			
	Mean	*SD*	Mean	*SD*	Mean change	*p* value[a]	β	95% CI Lower	95% CI Upper	*p* value[b]
Weight (kg)	84.48	14.65	84.27	15.34	-0.21	0.508	−0.21	−0.41	0.84	0.501
BMI (kg/m^2)	31.23	4.21	31.26	4.54	−0.03	0.814	0.03	−0.23	0.30	0.812
Waist circumference (cm)	102.47	10.11	102.65	11.00	0.19	0.744	0.19	−0.91	1.28	0.741
Metabolic parameters										
Fasting glucose (mmol/L)	5.16	0.96	5.21	1.21	0.05	0.625	0.05	−0.14	0.23	0.620
HbA1c (%)	5.63	0.66	5.60	0.75	−0.03	0.509	−0.03	−0.10	0.05	0.502
Cholesterol (mmol/L)	4.88	0.97	4.60	0.94	−0.28	**0.002**	−0.28	−0.44	−0.11	**0.001**
HDL (mmol/L)	1.19	0.30	1.23	0.30	0.03	0.070	0.03	0.00	0.06	0.062
LDL (mmol/L)	2.83	0.78	2.65	0.78	−0.16	0.051	−0.17	−0.33	−0.01	**0.038**
Triglycerides (mmol/L)	2.07	1.34	1.79	1.16	−0.28	**0.007**	−0.28	−0.47	−0.08	**0.005**
Neurocognition tests										
Symbol coding test	44.40	10.98	45.80	11.90	1.40	0.136	1.40	−0.40	3.20	0.127
Digit span	16.89	4.07	16.69	3.40	−0.20	0.552	−0.20	−0.85	0.45	0.545
Clinical scales										
GAF total	67.87	8.73	72.91	8.31	5.04	<**0.001**	5.04	2.93	7.14	<**0.001**
CGI-S	2.24	0.77	2.02	0.73	-0.22	**0.022**	−0.22	−0.40	−0.04	**0.017**
CGI-I	2.15	0.80	2.35	1.11	0.17	0.290	0.15	−0.14	0.44	0.300
PANSS total	48.53	9.26	49.36	11.20	0.84	0.484	0.84	−1.47	3.14	0.477
WHODAS	20.35	7.13	20.61	8.24	0.27	0.535	0.45	−1.34	2.25	0.621

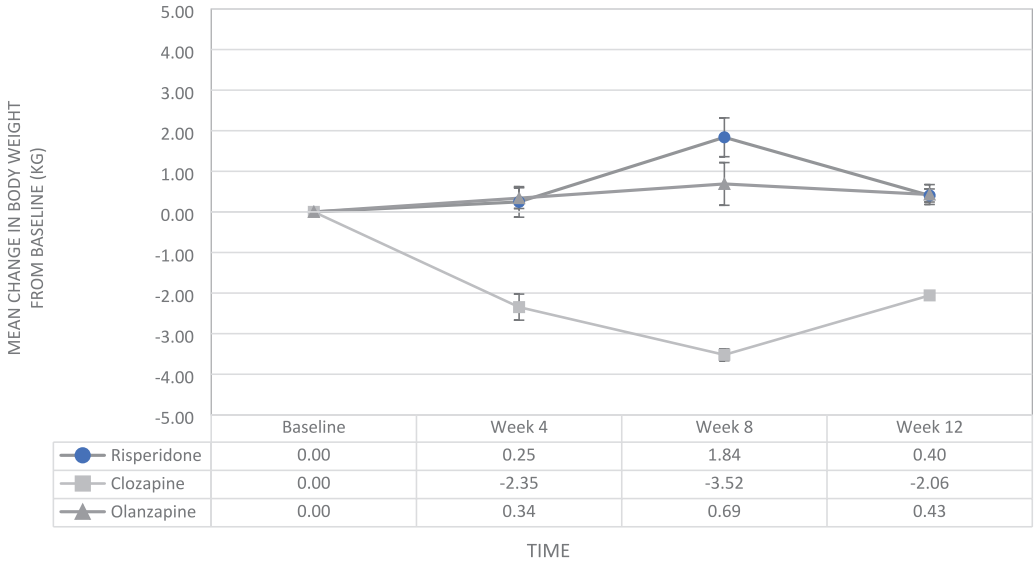
β: beta coefficient; CI: confidence interval; BMI: body mass index; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; GAF: Global Assessment of Functioning; CGI-S: Clinical Global Impression–Severity; CGI-I: Clinical Global Impression–Improvement; PANSS: Positive and Negative Syndrome Scale; WHODAS: World Health Organization Disability Assessment Scale.
[a]Paired *t* test.
[b]Age, sex, dosage and baseline measurements as covariates.
Bold values denote statistical significance at the $p < 0.05$

subjects (10.9%) had baseline scores >1 (median, 1; range, 1–2), while at visit 4, three subjects (5.5%) had scores >1 (median, 1; range. 1–2). For SAS, eight subjects (14.5%) had scores > 0 at baseline (median, 1; range, 1–2), while four subjects (7.5%) had scores > 0 (median, 2; range, 1–3).

Groupwise analyses

In groupwise analyses, only the group on clozapine had significant weight loss ($\beta = -2.06$, $p = 0.002$) after 12 weeks of adjunctive aripiprazole (see Figure 2). The clozapine group also had significant improvements in total cholesterol ($\beta = -0.47$, $p < 0.001$), HDL ($\beta = 0.08$, $p = 0.016$), LDL ($\beta = -0.28$, $p = 0.044$) and triglycerides ($\beta = -0.58$, $p = 0.038$). There were significant improvements in symptom severity ($\beta = -0.43$, $p = 0.010$) and functioning ($\beta = 8.29$, $p < 0.001$) (see Table 4).

The olanzapine group reported significant improvement in triglycerides ($\beta = -0.34$, $p = 0.001$); the



	Baseline	Week 4	Week 8	Week 12
Risperidone	0.00	0.25	1.84	0.40
Clozapine	0.00	-2.35	-3.52	-2.06
Olanzapine	0.00	0.34	0.69	0.43

Figure 2. Mean change in body weight (kg) from baseline for atypicals (olanzapine, risperidone and clozapine) and adjunct aripiprazole 5 mg.

other metabolic parameters showed similar improvement trends, but did not reach statistical significance (see Table 3). In the clinical measures, there was a significant improvement in functioning ($\beta = 4.33$, $p = 0.015$), but no significant change in symptom severity.

In the risperidone group, there were no significant changes to any metabolic indicators except the BMI, which increased from baseline to end of the study ($\beta = -0.39$, $p = 0.019$); however, there were significant improvements in symptom severity ($\beta = -0.30$, $p = 0.039$) and functioning ($\beta = 3.61$, $p = 0.022$) (see Table 5).

Discussion

This study was initiated to identify an effective and pragmatic strategy to tackle the growing epidemic of MetS associated with the use of atypical antipsychotics in schizophrenia.[45] Although our study found no significant weight reduction with adjunctive use of aripiprazole after 12 weeks, there were significant improvements in total cholesterol, LDL and triglycerides. The fixed dose of 5 mg aripiprazole was tolerated well and did not lead to side effects for the majority of the patients within the trial. The study also highlighted between group differences in favour of adjunctive aripiprazole use in individuals on olanzapine and clozapine, the two antipsychotics that are deemed more 'atypical' and most often associated with metabolic abnormalities (see Table 6).

The group on clozapine appears to benefit most from adjunctive use of aripiprazole. An improvement in lipid profile and weight but no significant change in the fasting glucose levels was also seen in previous trials with aripiprazole and clozapine.[32,33,46] It is likely that the duration of the study was too short for detecting the small change in glucose levels, as a similar study combining metformin and atypical antipsychotics for weight loss also did not detect a significant change in fasting glucose.[47] Importantly, 13 out of the 14 patients on clozapine achieved weight reduction in this 12-week trial, adding support to the adjunctive use of aripiprazole to clozapine for weight loss and improvement in metabolic profile.

Our study results do not make a case for use of fixed low-dose adjunct aripiprazole for olanzapine and risperidone patients as there was no weight loss. However, there was a significant reduction in triglycerides and increase in HDL levels that did not reach significance in the olanzapine group. These results are consistent with reports indicating improvements in triglycerides, but we did not observe the corresponding weight loss effects.[34,35] Taken together, the evidence does suggest improvement in cardiometabolic risk profile in individuals on olanzapine as hypertriglyceridaemia is an independent risk factor for cardiovascular disease.[48]

Aripiprazole is described as a partial agonist at D2 receptors although its complex mechanism of

Table 3. Mean change in weight and other outcomes between baseline and 12-week follow-up within olanzapine ($n = 18$).

	Baseline		12-week		Paired *t* test		Generalised estimating equations			
	Mean	*SD*	Mean	*SD*	Mean change	*p* value[a]	β	95% CI Lower	95% CI Upper	*p* value[b]
Weight (kg)	81.56	16.58	81.99	17.62	0.43	0.352	0.43	−0.42	1.28	0.325
BMI (kg/m^2)	30.24	4.21	30.31	4.44	−0.07	0.695	0.07	−0.27	0.42	0.681
Waist circumference (cm)	97.94	9.52	98.67	11.06	0.73	0.530	0.73	−1.44	2.89	0.510
Metabolic parameters										
Fasting glucose (mmol/L)	4.95	0.38	5.10	0.53	0.15	0.247	0.15	−0.09	0.39	0.217
HbA1c (%)	5.54	0.38	5.53	0.44	−0.01	0.926	−0.01	−0.12	0.11	0.922
Cholesterol (mmol/L)	5.12	1.16	4.94	1.15	−0.18	0.167	−0.18	−0.41	0.06	0.138
HDL (mmol/L)	1.19	0.26	3.06	0.92	0.05	0.105	0.05	−0.01	0.11	0.079
LDL (mmol/L)	3.13	0.92	1.24	0.30	−0.07	0.491	−0.07	−0.27	0.13	0.469
Triglycerides (mmol/L)	1.77	0.81	1.43	0.59	−0.34	**0.006**	−0.34	−0.55	−0.14	**0.001**
Neurocognition tests										
Symbol coding	45.94	10.23	47.83	10.61	1.89	0.302	1.89	−1.49	5.27	0.273
Digit span	16.83	4.16	16.39	3.50	−0.44	0.420	−0.44	−1.47	0.58	0.395
Clinical scales										
GAF total	69.11	7.44	73.44	7.51	4.33	**0.030**	4.33	0.85	7.82	**0.015**
CGI-S	2.11	0.47	2.17	0.71	0.06	0.749	0.06	−0.27	0.38	0.738
CGI-I	2.00	0.50	1.94	0.80	0.00	1.000	−0.02	−0.30	0.27	0.914
PANSS total	46.89	9.47	47.89	9.69	1.00	0.627	1.00	−2.85	4.85	0.611
WHODAS	23.06	9.14	22.35	10.65	0.12	0.948	−0.05	−3.42	3.32	0.977

β: beta coefficient; CI: confidence interval; BMI: body mass index; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; GAF: Global Assessment of Functioning; CGI-S: Clinical Global Impression–Severity; CGI-I: Clinical Global Impression–Improvement; PANSS: Positive and Negative Syndrome Scale; WHODAS: World Health Organization Disability Assessment Scale.
[a]Paired *t* test.
[b]Age, sex, dosage and baseline measurements as covariates.
Bold values denote statistical significance at the $p < 0.05$

action based on findings of large variations in both intrinsic activity and potency also suggests that aripiprazole is 'functionally selective' at D2 receptors.[49–51] Aripiprazole also works as a partial agonist at the serotonin 5-HT$_{1A}$ and 5-HT$_{2C}$ receptors and as an antagonist at the serotonin 5-HT$_{2A}$ receptor.[52] Dopamine D2 agonists are reported to reduce food intake by acting on hypothalamic areas,[53] while agonism of 5-HT$_{2C}$ receptors has been linked with decreased appetite and weight loss.[54] 5-HT$_{2C}$ receptors may also play a role in the peripheral dysregulation of leptin and ghrelin pathways and may impair neural processing of glucose and fat metabolism.[55]

Adjunctive use of aripiprazole in individuals on clozapine significantly improved clinical symptoms and functioning. Effectiveness of clozapine–aripiprazole combination in clozapine-resistant individuals has previously been reported[33] and is one of the strategies recommended by an expert consensus group.[56] This study findings are congruent with what was previously reported on this topic. At minimum, we do not observe any relapse or significant worsening of psychotic symptoms with the adjunctive use of aripiprazole.

Aripiprazole functions as a partial D2 agonist at mesocortical pathway, where reduced dopaminergic

Table 4. Mean change in weight and other outcomes between baseline and 12-week follow-up within clozapine ($n = 14$).

	Baseline		12-week		Paired *t* test		Generalised estimating equations			
	Mean	*SD*	Mean	*SD*	Mean change	*p* value[a]	β	95% CI Lower	95% CI Upper	*p* value[b]
Weight (kg)	84.22	12.50	82.16	12.32	−2.06	**0.010**	−2.06	−3.34	−0.78	**0.002**
BMI (kg/m^2)	31.01	3.10	30.40	3.48	0.61	0.072	−0.61	−1.20	−0.02	**0.042**
Waist circumference (cm)	104.86	10.44	103.95	11.28	−0.91	0.479	−0.91	−3.26	1.44	0.449
Metabolic parameters										
Fasting glucose (mmol/L)	4.89	0.31	4.84	0.39	−0.05	0.519	−0.05	−0.19	0.09	0.491
HbA1c (%)	5.29	0.33	5.21	0.30	−0.08	0.159	−0.08	−0.18	0.02	0.121
Cholesterol (mmol/L)	4.82	0.85	4.35	0.78	−0.47	**0.002**	−0.47	−0.71	−0.23	**<0.0001**
HDL (mmol/L)	1.11	0.17	2.29	0.55	0.08	**0.037**	0.08	0.01	0.14	**0.016**
LDL (mmol/L)	2.57	0.53	1.19	0.21	−0.27	0.094	−0.28	−0.54	−0.01	**0.044**
Triglycerides (mmol/L)	2.95	1.85	2.37	1.75	−0.58	0.066	−0.58	−1.13	−0.03	**0.038**
Neurocognition tests										
Symbol coding	49.50	13.55	49.00	14.28	−0.50	0.782	−0.50	−3.84	2.84	0.769
Digit span	16.00	2.99	16.00	3.21	0.00	1.000	0.00	−1.17	1.17	1.000
Clinical scales										
GAF total	62.43	9.76	70.71	9.64	8.29	**0.003**	8.29	4.01	12.56	**< 0.001**
CGIS	2.57	0.94	2.14	0.77	−0.43	**0.028**	−0.43	−0.75	−0.10	**0.010**
CGII	3.00	1.00	3.00	1.18	0.00	1.000	0.22	−0.85	1.29	0.687
PANSS total	53.93	8.86	55.21	12.94	1.29	0.640	1.29	−3.78	6.35	0.619
WHODAS	21.00	4.85	21.86	7.93	0.86	0.712	0.86	−3.43	5.15	0.696

β: beta coefficient; CI: confidence interval; BMI: body mass index; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; GAF: Global Assessment of Functioning; CGI-S: Clinical Global Impression–Severity; CGI-I: Clinical Global Impression–Improvement; PANSS: Positive and Negative Syndrome Scale; WHODAS: World Health Organization Disability Assessment Scale.
[a]Paired *t* test.
[b]Age, sex, dosage and baseline measurements as covariates.
Bold values denote statistical significance at the $p < 0.05$

activity is proposed to lead to negative symptoms and cognitive impairment.[57] While an 8-week open-label trial of aripiprazole's effect on cognition showed significant improvement in several neurocognitive domains and PANSS scores,[58] adjunct use of aripiprazole in a 24-week double-blind randomised placebo-controlled trial study, that added 10–15 mg aripiprazole to clozapine, found no significant effect on negative symptoms and executive cognitive functions.[59] In our study too, we did not see any significant changes in scores within the two neuropsychological tests of digit span and symbol coding and the PANSS scores.

Current treatment guidelines are usually critical of antipsychotic polypharmacy, with strong recommendation for monotherapy. However, in the case of aripiprazole, there seems to be evidence supporting its use as an adjunct, for its clinical effectiveness or improving metabolic risks.[46] In addition, adjunctive use of aripiprazole has also been recommended to reduce hyperprolactinaemia in patients on risperidone and other prolactin-raising antipsychotics[52] and for reduction in obsessive compulsive symptoms for patients on clozapine and olanzapine.[60,61]

Table 5. Mean change in weight and other outcomes between baseline and 12-week follow up within risperidone ($n = 23$).

	Baseline		12-week		Paired t-test		Generalised estimating equations			
	Mean	*SD*	Mean	*SD*	Mean change	*p* value[a]	β	95% CI Lower	95% CI Upper	*p* value[b]
Weight (kg)	86.93	14.44	87.33	15.21	0.40	0.372	0.40	−0.45	1.26	0.352
BMI (kg/m^2)	32.13	4.74	32.53	5.02	−0.39	0.056	0.39	16.30	48.69	**0.039**
Waist circumference (cm)	104.56	9.56	104.98	10.38	0.43	0.550	0.43	−0.92	1.77	0.535
Metabolic parameters										
Fasting glucose (mmol/L)	5.49	1.37	5.52	1.75	0.03	0.900	0.03	−0.37	0.42	0.897
HbA1c (%)	5.90	0.86	5.89	0.99	−0.01	0.907	−0.01	−0.15	0.13	0.904
Cholesterol (mmol/L)	4.73	0.87	4.50	0.81	−0.23	0.147	−0.23	−0.53	0.06	0.124
HDL (mmol/L)	1.25	0.38	2.53	0.62	−0.01	0.699	−0.01	−0.06	0.04	0.688
LDL (mmol/L)	2.71	0.70	1.24	0.35	−0.19	0.245	−0.19	−0.49	0.11	0.221
Triglycerides (mmol/L)	1.76	1.10	1.73	0.95	−0.04	0.754	−0.04	−0.27	0.19	0.745
Neurocognition tests										
Symbol coding	40.09	8.30	42.26	10.82	2.17	0.125	2.17	−0.44	4.79	0.103
Digit span	17.48	4.59	17.35	3.46	−0.13	0.824	−0.13	−1.24	0.98	0.818
Clinical scales										
GAF total	70.22	7.90	73.83	8.18	3.61	**0.036**	3.61	0.52	6.70	**0.022**
CGIS	2.13	0.81	1.83	0.72	−0.30	**0.031**	−0.30	−0.56	−0.05	**0.019**
CGII	1.91	0.68	2.26	1.14	0.36	0.119	0.36	−0.06	0.78	0.096
PANSS total	46.52	8.36	46.96	10.32	0.43	0.810	0.43	−2.99	3.86	0.804
WHODAS	17.83	5.79	18.57	6.00	0.74	0.508	0.74	−1.37	2.84	0.491

β: beta coefficient; CI: confidence interval; BMI: body mass index; HbA1c: haemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; GAF: Global Assessment of Functioning; CGI-S: Clinical Global Impression–Severity; CGI-I: Clinical Global Impression–Improvement; PANSS: Positive and Negative Syndrome Scale; WHODAS: World Health Organization Disability Assessment Scale.
[a]Paired *t* test.
[b]Age, sex, dosage and baseline measurements as covariates.
Bold values denote statistical significance at the $p < 0.05$

There are several limitations to this study. First, the overall sample size is small, particularly as the study included three different atypical antipsychotics, with distinct pharmacological profiles. The study used a fixed dose of 5 mg of aripiprazole, which is lowest among the published studies that have mostly used a variable dosing strategy (up to 20 mg daily).[62] A low fixed dose strategy reduces the likelihood of AEs and increases acceptability, yet it may have been inadequate to achieve significant improvement. The duration of the study was 12 weeks, which may not be sufficiently long to see significant change in the outcomes. The study did not identify patients who were pre-morbidly obese; thus, the study may have included patients whose weight gain was not linked to atypical antipsychotics. Concurrent medications like mood stabilisers may have contributed to weight and metabolic profile changes. Last but not least, this is an open-label study which lacks randomisation, placebo control and blinding.

Table 6. Side effects (frequency and severity) from use of adjunct aripiprazole with atypical antipsychotics olanzapine, clozapine and risperidone.

Side effect	Frequency	Severity
Anxiety	4	Mild
Dizziness	3	Mild
Sedation	3	Mild
Nausea	3	Mild-2, moderate-1
Increased appetite	3	Mild
Restlessness	2	Mild
Dystonia	2	Mild-1, moderate-1
Somnolence	2	Mild
Dry mouth	2	Mild-1, moderate-1
Insomnia	1	Moderate
Depression	1	Mild
Tremor	1	Mild
Headache	1	Severe
Blurred vision	1	Mild
Vomiting	1	Moderate
Constipation	1	Mild
Salivary hypersecretion	1	Moderate
Fatigue	1	Mild
Rash	1	Mild
Shortness of breath	1	Mild
Reduced appetite	1	Mild
Urinary frequency	1	Mild
Confusion	1	Moderate

Nonetheless, this study is an independent pragmatic trial, closely aligned to clinical practice and with broad inclusion criteria. The outcomes of the study are mostly objective (weight measurement and laboratory parameters), reducing the likelihood of bias. The other strengths of the study include the relatively low dropout rate. This may be the first open-label study aiming to assess the effect of adjunctive aripiprazole for weight reduction and improvement in metabolic profiles comparing the atypical antipsychotics risperidone, olanzapine and clozapine.

In conclusion, the results from this study support the adjunctive use of aripiprazole in individuals on clozapine and olanzapine in a bid to improve metabolic profile. Further studies on long-term effects of adjunctive aripiprazole to atypical antipsychotics are required to examine the sustainability of gains from early use as well

as long-term safety and tolerability of antipsychotic polypharmacy.

Conflict of interest statement

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References

1. Keepers GA, Fochtmann LJ, Anzia JM, *et al.* The American psychiatric association practice guideline for the treatment of patients with schizophrenia. *Am J Psych* 2020; 177: 868–872.
2. Meltzer HY and Gadaleta E. Contrasting typical and atypical antipsychotic drugs. *Focus* 2021; 19: 3–13.
3. Carli M, Kolachalam S, Longoni B, *et al.* Atypical antipsychotics and metabolic syndrome: from molecular mechanisms to clinical differences. *Pharmaceuticals* 2021; 14: 238.
4. Huhn M, Nikolakopoulou A, Schneider-Thoma J, *et al.* Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 2019; 394: 939–951.
5. Leucht S, Cipriani A, Spineli L, *et al.* Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013; 382: 951–962.
6. Grinchii D and Dremencov E. Mechanism of action of atypical antipsychotic drugs in mood disorders. *Int J Mol Sci* 2020; 21: 9532.
7. Gaviria AM, Franco JG, Aguado V, *et al.* A non-interventional naturalistic study of the prescription patterns of antipsychotics in patients with schizophrenia from the Spanish province of Tarragona. *PLoS ONE* 2015; 10: e0139403.
8. Marston L, Nazareth I, Petersen I, *et al.* Prescribing of antipsychotics in UK primary care: a cohort study. *BMJ Open* 2014; 4: e006135.
9. Keating D, McWilliams S, Boland F, *et al.* Prescribing pattern of antipsychotic medication for first-episode psychosis: a retrospective cohort study. *BMJ Open* 2021; 11: e040387.
10. Park S-C, Lee M-S, Kang S-G, *et al.* Patterns of antipsychotic prescription to patients with schizophrenia in Korea: results from the health insurance review & assessment service-national patient sample. *J Korean Med Sci* 2014; 29: 719–728.
11. Seshadri M, Elsemary A, Thalitaya MD, *et al.* Study on the prescribing patterns of antipsychotic medication in a rural England Community Mental Health Team. *Psychiatr Danub* 2017; 29: 524–529.
12. Aringhieri S, Carli M, Kolachalam S, *et al.* Molecular targets of atypical antipsychotics: from mechanism of action to clinical differences. *Pharmacol Ther* 2018; 192: 20–41.
13. Lee J, Nurjono M, Wong A, *et al.* Prevalence of metabolic syndrome among patients with schizophrenia in Singapore. *Ann Acad Med Singap* 2012; 41: 457–462.
14. Vancampfort D, Stubbs B, Mitchell AJ, *et al.* Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry* 2015; 14: 339–347.
15. McCracken E, Monaghan M and Sreenivasan S. Pathophysiology of the metabolic syndrome. *Clin Dermatol* 2018; 36: 14–20.
16. Mottillo S, Filion KB, Genest J, *et al.* The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 56: 1113–1132.
17. Regufe VM, Pinto CM and Perez PMVHC. Metabolic syndrome in type 2 diabetic patients: a review of current evidence. *Porto Biomed J* 2020; 5: e101.
18. Association AD. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27: 596–601.
19. De Hert M, Detraux J, Van Winkel R, *et al.* Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2012; 8: 114–126.

20. Perez Rodriguez A, Tajima-Pozo K, Lewczuk A, *et al.* Atypical antipsychotics and metabolic syndrome. *Cardiovasc Endocrinol* 2015; 4: 132–137.
21. Papanastasiou E. The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. *Ther Adv Psychopharmacol* 2013; 3: 33–51.
22. Tumiel E, Wichniak A, Jarema M, *et al.* Nonpharmacological interventions for the treatment of cardiometabolic risk factors in people with schizophrenia – a systematic review. *Front Psychiatry* 2019; 10: 566.
23. Cooper SJ, Reynolds GP, Barnes T, *et al.* BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *J Psychopharmacol* 2016; 30: 717–748.
24. Stroup TS, McEvoy JP, Ring KD, *et al.* A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry* 2011; 168: 947–956.
25. Stroup TS, Byerly MJ, Nasrallah HA, *et al.* Effects of switching from olanzapine, quetiapine, and risperidone to aripiprazole on 10-year coronary heart disease risk and metabolic syndrome status: results from a randomized controlled trial. *Schizophr Res* 2013; 146: 190–195.
26. Newcomer JW, Campos JA, Marcus RN, *et al.* A multicenter, randomized, double-blind study of the effects of aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder switched from olanzapine. *J Clin Psychiatry* 2008; 69: 1046–1056.
27. Weiden PJ. Switching antipsychotics as a treatment strategy for antipsychotic-induced weight gain and dyslipidemia. *J Clin Psychiatry* 2007; 68: 34–39.
28. Citrome L. A systematic review of meta-analyses of the efficacy of oral atypical antipsychotics for the treatment of adult patients with schizophrenia. *Expert Opin Pharmacother* 2012; 13: 1545–1573.
29. Meyer JM, Davis VG, Goff DC, *et al.* Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res* 2008; 101: 273–286.
30. Rummel-Kluge C, Komossa K, Schwarz S, *et al.* Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2010; 123: 225–233.
31. Fleischhacker WW, Heikkinen ME, Olié JP, *et al.* Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: a randomized, double-blind, placebo-controlled trial. *Int J Neuropsychopharmacol* 2010; 13: 1115–1125.
32. Fan X, Borba CP, Copeland P, *et al.* Metabolic effects of adjunctive aripiprazole in clozapine-treated patients with schizophrenia. *Acta Psychiatr Scand* 2013; 127: 217–226.
33. Chang JS, Ahn Y, Park HJ, *et al.* Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2008; 69: 720–731.
34. Henderson DC, Fan X, Copeland PM, *et al.* Aripiprazole added to overweight and obese olanzapine-treated schizophrenia patients. *J Clin Psychopharmacol* 2009; 29: 165–169.
35. Wang L-J, Ree S-C, Huang Y-S, *et al.* Adjunctive effects of aripiprazole on metabolic profiles: comparison of patients treated with olanzapine to patients treated with other atypical antipsychotic drugs. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; 40: 260–266.
36. Mizuno Y, Suzuki T, Nakagawa A, *et al.* Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull* 2014; 40: 1385–1403.
37. Taylor DM, Barnes TR and Young AH. *The Maudsley prescribing guidelines in psychiatry*. Newark, NJ: John Wiley & Sons, 2021.
38. Galling B, Roldan A, Hagi K, *et al.* Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. *World Psychiatry* 2017; 16: 77–89.
39. Gupta B, LYS Chua, Ong J, Verma SK, Tan GCY, *et al.* Aripiprazole as an adjunct for weight loss in patient's established on clozapine and olanzapine. In: *Singapore health and biomedical congress*, Singapore, 2& 3rd October 2015, p. S315. Singapore: Annals of the Academy of Medicine.
40. Kay SR, Opler LA and Lindenmayer JP. The positive and negative syndrome scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl* 1989; 7: 59–67.

41. Guy W, editor. Clinician global impression (CGI). In: *ECDEU assessment manual for psychopharmacology*. US Department of Health, Education, and Welfare Publication (ADM). Rockville, MD: National Institute of Mental Health, 1976, pp. 76–338.

42. Association AP. *Diagnostic criteria from DSM-IV-TR*. Washington, DC: American Psychiatric Publishing, 2000.

43. Üstün TB, Kostanjsek N, Chatterji S, *et al. Measuring health and disability: manual for WHO disability assessment schedule WHODAS 2.0*. Geneva: World Health Organization, 2010.

44. Fervaha G, Agid O, Foussias G, *et al.* Toward a more parsimonious assessment of neurocognition in schizophrenia: a 10-minute assessment tool. *J Psychiatr Res* 2014; 52: 50–56.

45. Pramyothin P and Khaodhiar L. Metabolic syndrome with the atypical antipsychotics. *Curr Opin Endocrinol Diabetes Obes* 2010; 17: 460–466.

46. Fleischhacker WW and Uchida H. Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. *Int J Neuropsychopharmacol* 2014; 17: 1083–1093.

47. Wang M, Tong J-H, Zhu G, *et al.* Metformin for treatment of antipsychotic-induced weight gain: a randomized, placebo-controlled study. *Schizophr Res* 2012; 138: 54–57.

48. Boullart A, de Graaf J and Stalenhoef AF. Serum triglycerides and risk of cardiovascular disease. *Biochim Biophys Acta* 2012; 1821: 867–875.

49. Mailman RB and Murthy V. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? *Curr Pharm Des* 2010; 16: 488–501.

50. de Bartolomeis A, Tomasetti C and Iasevoli F. Update on the mechanism of action of aripiprazole: translational insights into antipsychotic strategies beyond dopamine receptor antagonism. *CNS Drugs* 2015; 29: 773–799.

51. Tuplin EW and Holahan MR. Aripiprazole, a drug that displays partial agonism and functional selectivity. *Cur Neuropharmacol* 2017; 15: 1192–1207.

52. Shapiro DA, Renock S, Arrington E, *et al.* Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology* 2003; 28: 1400–1411.

53. Deng C, Chen J, Hu C, *et al.* What is the mechanism for aripiprazole's effect on reducing olanzapine-associated obesity? *J Clin Psychopharmacol* 2010; 30: 480–481.

54. Bickerdike MJ. 5-HT2C receptor agonists as potential drugs for the treatment of obesity. *Curr Top Med Chem* 2003; 3: 885–897.

55. Nonogaki K, Nozue K and Oka Y. Hyperphagia alters expression of hypothalamic 5-HT2C and 5-HT1B receptor genes and plasma des-acyl ghrelin levels in Ay mice. *Endocrinology* 2006; 147: 5893–5900.

56. Wagner E, Kane JM, Correll CU, *et al.* Clozapine combination and augmentation strategies in patients with schizophrenia – recommendations from an international expert survey among the treatment response and resistance in psychosis (TRRIP) working group. *Schizophr Bull* 2020; 46: 1459–1470.

57. Mitsonis CI, Dimopoulos NP, Mitropoulos PA, *et al.* Aripiprazole augmentation in the management of residual symptoms in clozapine-treated outpatients with chronic schizophrenia: an open-label pilot study. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31: 373–377.

58. Riedel M, Spellmann I, Schennach-Wolff R, *et al.* Effect of aripiprazole on cognition in the treatment of patients with schizophrenia. *Pharmacopsychiatry* 2010; 43: 50–57.

59. Muscatello MRA, Bruno A, Pandolfo G, *et al.* Effect of aripiprazole augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. *Schizophr Res* 2011; 127: 93–99.

60. Englisch S, Esslinger C, Inta D, *et al.* Clozapine-induced obsessive-compulsive syndromes improve in combination with aripiprazole. *Clin Neuropharmacol* 2009; 32: 227–229.

61. Schönfelder S, Schirmbeck F, Waltereit R, *et al.* Aripiprazole improves olanzapine-associated obsessive compulsive symptoms in schizophrenia. *Clin Neuropharmacol* 2011; 34: 256–257.

62. Zheng W, Zheng Y-J, Li X-B, *et al.* Efficacy and safety of adjunctive aripiprazole in schizophrenia: meta-analysis of randomized controlled trials. *J Clin Psychopharmacol* 2016; 36: 628–636.