Switching From 2 Antipsychotics to 1 Antipsychotic in Schizophrenia:
A Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Objective: Antipsychotic polypharmacy (APP) is employed routinely, although it remains controversial because robust evidence supporting its efficacy is lacking. In addition, it is associated with increased costs, higher antipsychotic dosing, and greater risk of side effects. Surprisingly, no prospective, randomized, double-blind studies have addressed this issue; the present investigation set out to fill this gap in knowledge.

Method: A 12-week, double-blind, randomized, placebo-controlled, single-site study was carried out in individuals with schizophrenia or schizoaffective disorder (*DSM-IV*) receiving a designated primary antipsychotic plus a secondary antipsychotic, with doses stabilized for each. Individuals were randomly assigned to APP (N = 17), reflecting current treatment, or antipsychotic monotherapy (APM) (N = 18), in which the secondary antipsychotic was discontinued. Assessments occurred weekly during month 1 and every 2 weeks during months 2 and 3; the primary outcome measure was the Brief Psychiatric Rating Scale (BPRS) total score. Other measures included the Clinical Global Impressions (CGI) scale, Simpson-Angus Scale, and Barnes Akathisia Scale. The study was carried out between August 2006 and March 2011.

Results: Withdrawal due to clinical deterioration occurred in 1 individual receiving APP (5.8%) and in 4 individuals in the APM group (22.2%). Overall, however, there was no indication of clinical worsening with APM, as measured using BPRS and CGI scale.

Conclusions: Almost 80% (n = 14) of individuals with schizophrenia or schizoaffective disorder currently receiving APP could be safely transitioned to APM with no clinical deterioration. For those who do deteriorate, risk appears greatest in the first several months. From another perspective, results also indicate that a minority of individuals benefit from APP, and research focusing on identifying this group may represent the best strategy to curb excessive use of APP.

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Best practice guidelines recommend antipsychotic monotherapy as the gold standard for schizophrenia and related disorders, while discouraging antipsychotic polypharmacy (APP) except as a last resort in the face of failure of clozapine.[1–3] In addition to the added cost attributed to coprescription of antipsychotic drugs,[2,4,5] the practice of APP has been associated with increased cognitive impairment[6] and other adverse effects,[2,6–10] escalating antipsychotic doses,[7,11,12] and increased duration of hospitalization. Antipsychotic polypharmacy is not only highly prevalent, but it is also increasing, with reported prevalence rates in excess of 20%.[7,13,14] Treatment resistance in schizophrenia and the various barriers that limit trials with clozapine both contribute to APP.[15] Regardless of the cause, though, the high health and economic costs of APP[4] call for closer scrutiny of this controversial practice, provocatively referred to as "psychiatry's dirty little secret."[16] A recent critical review of APP concluded that it is associated with increased mortality, metabolic syndrome, decreased cognitive functioning, high-dose prescription, and nonadherence.[17]

The practice of APP has been extensively reviewed recently, with inconclusive or mixed results. Several meta-analyses and reviews[18–22] have, for example, concluded that at least limited evidence supports the addition of a second antipsychotic to clozapine. In 1 of these meta-analyses[18] involving 19 randomized controlled studies, the authors concluded that APP may be superior to antipsychotic monotherapy (APM) in certain clinical situations such as acute psychosis where combinations are sometimes initiated together, in the context of clozapine augmentation, or in patients exposed to APP for periods exceeding 10 weeks. Similarly, a second meta-analysis[19] reported modest improvements in efficacy with clozapine combinations, but in only open-label studies. Relative to this point of combinations with clozapine, several systematic reviews[23,24] indicated a lack of evidence for APP in the case of coprescriptions of non-clozapine atypical antipsychotics. While low-dose APP has been associated with a comparatively decreased risk of prolactin elevation and metabolic side effects,[6] it remains that the clinical efficacy of APP has not been clearly established.[6,23]

Perhaps not so surprising is that once APP is established in the clinical care of difficult-to-treat patients, clinicians are understandably averse to reverting to APM, despite the observation that most clinicians do not believe that APP therapy benefits their patients.[25] Given the chronic relapsing nature of primary psychotic disorders, the coincidence of clinical stability in the context of concomitant antipsychotic therapy (eg, in the course of cross-titration) cannot be taken as confirmation of a cause-and-effect relationship.[26]

Evidence that can be used by clinicians to manage established APP is lacking. To date, only 2 studies[27,28] have addressed the maintenance

Clinical Points

- Antipsychotic polypharmacy (ie, taking more than 1 antipsychotic) is common although often criticized; however, controlled studies examining this controversial practice are limited.
- Using a double-blind, placebo-controlled design, the present study established that a number of individuals receiving antipsychotic polypharmacy can be transitioned to antipsychotic monotherapy without compromising clinical response.

of clinical stability in the context of switching from APP to APM in adults with schizophrenia and schizoaffective disorder. Findings from both support the notion that the majority of patients can be converted from 2 or more antipsychotics to 1 antipsychotic, with 1 study[27] reporting worsening in approximately 23% of patients; however, the design of these studies[27,28] was open-label and single-blind, respectively. To address these limitations, the present investigation was conducted to evaluate the reduction of APP to APM in schizophrenia and schizoaffective disorder using a double-blind design.

METHOD

Study Design

A 12-week, double-blind, randomized, placebo-controlled, single-site study (ClinicalTrials.gov identifier: NCT00493233) compared individuals with schizophrenia or schizoaffective disorder receiving a fixed dose of their prescribed secondary antipsychotic versus placebo in addition to their prescribed primary antipsychotic. The study was carried out at the Centre for Addiction and Mental Health (CAMH), an academic teaching psychiatric hospital associated with the University of Toronto, Ontario, Canada.

Study Participants

Participants were recruited and evaluated between August 2006 and March 2011. Referrals came through presentations to clinical staff, posted fliers within CAMH, and from the hospital pharmacy. As part of the screening process, all potential subjects were assessed for competence using the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR).[29] All subjects gave their written consent after the procedure had been fully explained; the study/recruitment procedures were approved by the Research Ethics Board of the Centre for Addiction and Mental Health.

Inclusion and Exclusion Criteria

Inclusion criteria included (1) outpatient or inpatient status; (2) ≥ 18 years of age; (3) *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, diagnosis of schizophrenia or schizoaffective disorder; and (4) taking 2 antipsychotic drugs for ≥ 30 days. Participants with a history of depot antipsychotic treatment within 6 months were excluded from the study unless the depot antipsychotic was considered the main antipsychotic drug. Prescribing history was reviewed by a pharmacist, and prospective participants with evidence of ongoing cross-titration of antipsychotic medication as part of switching agents, as well as use of prescribed antipsychotics on an as-needed basis, were also excluded.

Randomization

Eligible participants were randomly assigned to 1 of 2 groups: (1) continuation of regular regimen of prescribed primary antipsychotic and fixed dose of secondary antipsychotic or (2) continuation of primary antipsychotic and placebo. The primary antipsychotic was identified by the treating physician, except for clozapine and depot antipsychotics in which case it was assumed that they represented the primary antipsychotic. Dosing of the primary antipsychotic was flexible and could be increased or decreased at the clinical discretion of the patient's treating physician. Adjunctive or concomitant psychotropic medications other than antipsychotic medications were permitted.

Drug Regimen

Participants were randomly assigned through fixed-block randomization, conducted in a double-blind fashion. Pharmacy staff prepared matching capsules containing either the participant's secondary antipsychotic or placebo. The study medication was dispensed in blister packs on a weekly basis starting at week 1 (baseline) for 21 days and every 2 weeks thereafter until study completion at week 12 (day 77). Adherence with study medication was assessed at each study visit via pill count, which in previous work by our group has been identified as a reasonable proxy when compared to electronic monitoring.[30]

Ratings and Outcome Variables

For the purpose of diagnosis, the Mini-International Neuropsychiatric Interview (MINI)[31] version 5.0.0 and psychiatric history were employed. Structured evaluations monitoring clinical symptoms and side effects were conducted as follows: weekly for weeks 1–4 and every 2 weeks from weeks 4–12. Psychopathology was assessed using the 18-item Brief Psychiatric Rating Scale (BPRS)[32] and the Clinical Global Impressions (CGI) scale.[33] Presence of akathisia, parkinsonism, and tardive dyskinesia was assessed using the Barnes Akathisia Scale (BAS),[34] the Simpson-Angus Scale (SAS),[35] and the Abnormal Involuntary Movement Scale (AIMS).[33]

Statistical Analysis

Statistical analyses were carried out using the SAS System version 9.1.3. For comparison of the 2 groups with respect to age, gender, days in study, dropouts, primary antipsychotic dose (mg/d), and clinical scores at baseline (BPRS, CGI), the χ^2 test, Fisher exact test, and Student *t* test (2-tailed) were used as indicated. A series of mixed models were chosen to determine whether outcomes on BPRS and SAS scales changed differentially across the 2 study groups over the 12-week study. Maximum likelihood

Table 1. Demographics of Treatment Groups

Variable	Antipsychotic Polypharmacy (N = 17)	Antipsychotic Monotherapy (N = 18)
Dropouts, n (%)	2 (12)	5 (28)
Sex, n (%)		
Male	10 (59)	14 (78)
Female	7 (41)	4 (22)
Ethnicity, n (%)		
White	10 (59)	13 (72)
African	3 (18)	3 (17)
East/Southeast Asian	4 (24)	2 (11)
Age, median (range), y	48 (27–68)	47 (26–64)
Weight, median (range), kg	85 (44–122)	85 (61–122)
Smoking, n (%)	8 (47)	10 (56)
Days in study, median (range)	73 (2–77)	60 (11–78)
Concomitant medications		
Benzodiazepines, n (%)	10 (59)	7 (39)
Mood stabilizers, n (%)	6 (35)	4 (22)
Antidepressants, n (%)	7 (41)	4 (22)
Antiparkinsonians, n (%)	7 (41)	6 (33)
BPRS baseline mean score	35.70	32.94
CGI scale baseline mean score	4.3	3.7
Inpatient, n (%)	5 (29)	4 (22)
Age at first episode, median (range), y	23 (16–54)	19 (10–43)
Previous psychotic episodes, median (range)	8 (2–10)	5 (1–40)
Psychiatric hospitalizations in the last 2 years, n (%)		
Yes	8 (47)	9 (50)
No	9 (53)	9 (50)
Participant's belief of whether they remained on secondary antipsychotic, n (%)		
Yes	5 (29)	6 (33)
No	4 (24)	5 (28)
Don't know	6 (35)	5 (28)
Missing	2 (12)	2 (11)

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions.

was selected, and a series of potential covariance structures (variance components, compound symmetric, first-order autoregressive, heterogeneous compound symmetric, heterogeneous first-order autoregressive, and unstructured) were investigated.

A piecewise linear approach was applied to 2 separate "time" effects in each model: early effects (weeks 1–4) and late effects (>4 weeks) using linear curves known as splines (SAS System version 9.1.3). With this approach, the estimated model coefficients were able to determine whether group differences in outcomes occur early in follow-up, late in follow-up, during both phases, or not at all. Next, a series of linear contrasts were performed directly with the coefficients to test specific hypotheses about the magnitude of the group/time effects on our outcome measure. Time (week) was treated as a continuous variable. All analyses were carried out by using the raw data, and sensitivity analyses were conducted by using a last-observation-carried-forward approach. Fisher exact test was used to determine the number of participants whose CGI scores were better or worse at weeks 4 and 12 than at baseline, and these proportions were compared across study groups. Generalized estimating equations were used to analyze the presence or absence of binary outcomes (ie, AIMS-item 8 and BAS-item 4).

RESULTS

Sample Characteristics

In the study, 156 subjects expressed interest, of whom 106 met eligibility criteria and 56 signed consent. After the informed-consent procedure, a further 20 participants were either screen failures or declined proceeding to the randomization phase. The remaining 36 participants were randomly assigned to APP or APM. One randomized participant (APP) was excluded from data analysis due to withdrawal prior to the first dose of study medication. Baseline study characteristics of the 2 groups (APP and APM) are summarized in Table 1. At baseline, all participants were treated with a combination of 2 antipsychotics (Table 2), ie, the most common groupings included clozapine and risperidone (n = 5; 14%), clozapine and olanzapine (n = 4; 11%), quetiapine and haloperidol (n = 4; 11%), clozapine and haloperidol (n = 3; 9%), and clozapine and haloperidol (n = 3; 9%). In addition, there were 18 additional antipsychotic groupings. In the case of the APP group, duration of exposure to the primary antipsychotic ranged from 3 months to 40 years (mean ± SD = 234.25 ± 500.00 weeks), and the duration of exposure to the secondary antipsychotic ranged from 10 months to 4 years (mean ± SD = 183 ± 298 weeks). For those in the APM group, duration of exposure to the primary antipsychotic ranged from 2 months to 24 years (mean ± SD = 291.56 ± 361.90 weeks), and the duration of exposure to the secondary antipsychotic ranged from 5 months to 16 years (mean ± SD = 130.44 ± 185.00 weeks). Based on pill counts, recorded adherence for the secondary medication was 96.54% ± 6.82% and 94.60% ± 16.84% for the APP and APM samples, respectively, each exceeding the threshold of 70%–80% that is often used to define adherence.[36,37]

There were no differences between the APP and APM groups in terms of age ($P = .636$), gender ($P = .414$), baseline BPRS ($P = .483$), baseline CGI score ($P = .207$), and number of hospitalizations ($P = .422$). The calculated daily mean ± SD dose at baseline was not significantly different between the APP (241.02 ± 127.72 mg) and APM (328.74 ± 201.94 mg) groups ($P = .143$) and is in line with evidence of a gradual shift to lower antipsychotic dosing.[38–41] Dropout rates were not statistically different between the 2 groups ($P = .400$) or different as a function of gender ($P = .289$).

Dropout Characteristics in the Follow-Up Phase

Four participants in the APM group withdrew from the study (Table 1) within 1–6 weeks and had stopped taking their study medications from 2 to 32 days for clinical worsening that could be subtyped as follows: psychosis (n = 2, week 2 [day 2]; week 6 [day 32]), depression (n = 1, week 3 [day 14]), and aggression/anxiety (n = 1, week 3 [day 13]). All 4 participants were taking clozapine as a primary antipsychotic and olanzapine (n = 2), loxapine (n = 1), or haloperidol (n = 1) as their secondary antipsychotic. One additional APM participant taking zuclopenthixol decanoate and olanzapine was withdrawn from the study

Table 2. Baseline Antipsychotic Profile of Treatment Groups

	Polypharmacy (N = 17)		Monotherapy (N = 18)	
Antipsychotic Class	n	%	n	%
Atypical antipsychotic				
Primary	16	94	12	67
Secondary	10	59	11	61
Typical antipsychotic				
Primary	1	6	6	33
Secondary	7	41	7	39

	Primary		Secondary		Primary		Secondary	
Specific antipsychotic	n	%	n	%	n	%	n	%
Atypical								
Clozapine	8	47.1	0	0	7	38.9	0	0
Quetiapine	5	29.4	3	17.6	1	5.6	3	16.7
Olanzapine	2	11.8	2	11.8	2	11.1	6	33.3
Risperidone	1	5.9	5	29.4	2	11.1	2	11.1
Typical								
Flupenthixol decanoate	0	0	0	0	1	5.6	0	0
Haloperidol decanoate	0	0	0	0	1	5.6	0	0
Haloperidol	0	0	6	35.3	0	0	2	11.1
Fluphenazine decanoate	0	0	0	0	2	11.1	0	0
Pipotiazine palmitate	1	5.9	0	0	0	0	0	0
Zuclopenthixol decanoate	0	0	0	0	1	5.6	0	0
Perphenazine	0	0	0	0	1	5.6	0	0
Methotrimeprazine	0	0	0	0	0	0	2	11.1
Loxapine	0	0	1	5.9	0	0	3	16.7

(week 6 [day 35]) due to a protocol deviation (withdrawal of consent).

In the APP group, 1 participant taking clozapine and olanzapine was withdrawn from the study by the investigator (week 9 [day 50]) due to a protocol deviation (abscondment), and 1 participant taking olanzapine and haloperidol withdrew for clinical worsening (ie, increased sleep disturbance, week 3 [day 10]). The dropout participants in both groups were all male and between the ages of 26 and 51 years.

Primary Outcome: BPRS Total Score

Brief Psychiatric Rating Scale total scores for the 2 study groups are summarized in Table 3. As can be observed (Figure 1), the greatest difference in BPRS mean total scores was observed at week 1 (baseline), although this was not significant ($P = .17$). In line with this finding, though, the rate of decline in BPRS total scores during the early phase (weeks 1–4) was significantly greater in the APP group versus the APM group ($P = .02$). In the late phase (weeks 4–12), rate of change did not differ across study groups ($P = .77$).

Secondary Outcomes and Side Effects

Brief Psychiatric Rating Scale subscale scores (Thinking Disorder, Withdrawal/Retardation, Anxiety/Depression, Hostility/Suspiciousness, and Activation) were also analyzed. There were no significant differences in the baseline scores or in the magnitude of decline in Thinking Disorder and Hostility/Suspiciousness. Activation scores were higher in the APP group at baseline (week 1) when compared with the APM group ($P = .02$). Again, in keeping with higher total BPRS scores in the APP group at week 1, rate of decline during weeks 1–4 was greater in these individuals for Anxiety/Depression ($P = .04$) and Withdrawal/Retardation ($P < .0001$), while marginally greater for Thinking Disorder ($P = .06$). No other significant differences were found for subscale scores, including rate of change in the late phase.

Using Fisher exact test, we found the groups were comparable on CGI-Severity scores at weeks 4 ($P = .36$) and 12 ($P = .59$) compared to baseline. Similarly, Student *t* tests demonstrated similarity between the 2 groups in terms of CGI-Improvement scores at weeks 4 ($P = .52$) and 12 ($P = .35$) (Table 4).

Regarding side effects, there were no group differences at baseline or during the early ($P = .39$) or late ($P = .31$) phases for SAS total scores. This was also the case when the 2 groups were compared on item 8 (overall severity) of the AIMS where no abnormal movements were recorded in 88% of the assessments (n = 244) and item 4 (global score) of the BAS where no akathisia was recorded in 82% of the assessments (n = 249).

The aforementioned findings remained when sensitivity analyses were conducted for each of the outcome measures.

DISCUSSION

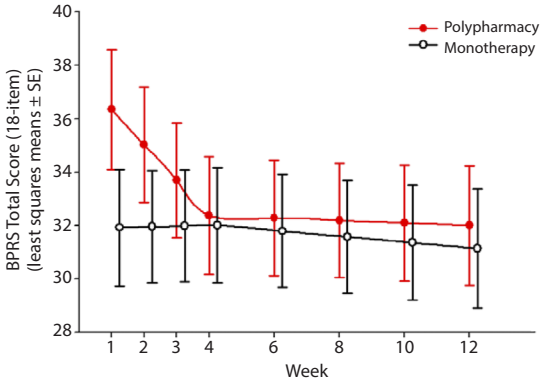
To our knowledge, this 12-week (77-day) study is the first trial using a prospective, double-blind, placebo-controlled design to investigate reducing APP to APM. Subjects were randomly assigned and not matched, although there were no differences in terms of age, gender, or baseline clinical scores (BPRS and CGI). Overall, the majority of participants tolerated the switch to APM without clinical worsening; indeed, the low all-cause discontinuation noted in this study captures this finding. Of note, in this particular investigation, those who remained on APP actually underwent a decrease in BPRS total scores that translated to a significant difference in rate of change when compared to those switched to APM. This was also seen in BPRS subscale scores, specifically Anxiety/Depression and Withdrawal/Retardation; however, this difference disappeared during weeks 4–12. That this greater decrease in BPRS scores during weeks 1–4 could be interpreted as APP's clinical superiority must be viewed with caution for several reasons. Those in the APP group (vs the APM group) had a higher BPRS total score (35.7 vs 32.9) and a higher CGI score (4.3 vs 3.7) at week 1, albeit nonsignificant. In addition, the magnitude of decrease was in the range of only 2 points, which amounts to a reduction in BPRS total score of approximately 5% and possibly reflects regression to the mean.

It does warrant comment that 4 individuals in the APM group withdrew for reasons related to clinical worsening, compared to 1 in the APP group. All 4 dropouts withdrew within the first 32 days, suggesting that those who will not do well with a switch to APM are likely to declare themselves in the first weeks after the change has been made. This difference between the APP and APM groups early in treatment also calls into question the study's design, which introduced the switch

Table 3. Comparison of Antipsychotic Polypharmacy Versus Monotherapy on Brief Psychiatric Rating Scale (BPRS) 18-Item Scores

BPRS Score	Week 1 (Day 1)	Weeks 1–4 (Days 1–21) Change During Early Interval	Week 4 (Day 21)	Weeks 4–12 (Days 21–77) Change During Late Interval
Total				
Estimate	−4.42	1.35	−0.17	−0.06
SE	3.13	0.56	3.31	0.22
95% CI	(−10.79 to 1.95)	(0.24 to 2.46)	(−6.70 to 6.36)	(−0.49 to 0.36)
P value	.17	.02	.96	.77
Thinking disorder				
Estimate	−2.39	−0.56	−0.5	−0.07
SE	2.06	0.3	2.14	0.12
95% CI	(−6.57 to 1.80)	(−0.03 to 1.15)	(−4.71 to 3.72)	(−0.30 to 0.16)
P value	.25	.06	.81	.55
Withdrawal/retardation				
Estimate	−3.11	0.99	0.2	−0.11
SE	1.24	0.22	1.31	0.08
95% CI	(−5.63 to −0.59)	(0.56 to 1.42)	(−2.37 to 2.78)	(−0.30 to 0.05)
P value	.02	< .0001	.88	.17
Anxiety/depression				
Estimate	−1.31	0.53	0.18	0.03
SE	0.86	0.26	0.99	0.1
95% CI	(−3.06 to 0.45)	(0.02 to 1.04)	(−1.78 to 2.14)	(−0.16 to 0.23)
P value	.14	.04	.86	.75
Hostility/suspiciousness				
Estimate	−0.73	0.21	−0.05	−0.02
SE	0.94	0.21	1.03	0.08
95% CI	(−2.65 to 1.18)	(−0.21 to 0.63)	(−2.07 to 1.98)	(−0.18 to 0.15)
P value	.44	.32	.96	.85
Activation				
Estimate	−0.96	0.27	−0.12	−0.01
SE	0.37	0.17	0.53	0.07
95% CI	(−1.72 to −0.21)	(−0.07 to 0.61)	(−1.17 to 0.93)	(−0.15 to 0.13)
P value	.01	.12	.82	.89

Figure 1. Change in Total Brief Psychiatric Rating Scale (BPRS) Score During 12 Weeks for Antipsychotic Polypharmacy Versus Monotherapy



to APM through abrupt discontinuation of the secondary antipsychotic, as compared to a crossover and gradual tapering approach that often takes place in clinical practice.[42] While a meta-analysis failed to substantiate differences between the 2 switching strategies in longer-term outcome,[43] there is evidence that increased adverse effects can occur with abrupt switching.[44] This could reflect either withdrawal symptoms in conjunction with antipsychotic discontinuation[45] or possible symptom exacerbation following withdrawal of the second antipsychotic. Unfortunately, we did not include a more global side-effect scale, such as the Udvalg for Kliniske Undersøgelser,[46] which might have allowed this question to be examined more closely. It is worth pointing out that all 4 subjects in the APM group withdrawn for clinical worsening were taking clozapine as the primary antipsychotic, with the caveat that clozapine represented the primary antipsychotic in almost 40% of this sample (Table 2). This does raise the possibility that a specific clinical subpopulation, ie, "ultraresistant" or clozapine partial responders,[47] is more vulnerable, which is in line with recent reviews[23,48,49] concluding that the value of clozapine augmentation cannot be dismissed categorically.

Notwithstanding those who were withdrawn, no significant differences between the 2 groups were identified on the basis of CGI-Severity or -Improvement scores at either week 4 or 12. Also noteworthy is that, while the study design allowed for flexible dose titration of the first antipsychotic by the treating physician, most physicians did not exercise this option, suggesting that more often than not, subjects could be maintained on APM without upward dose titration to accommodate the discontinuation of the secondary antipsychotic.

Our data are consistent with those from 2 previous studies[27,28] in which patients transitioned from APP to APM. The first[27] represents a 6-month open-label study of 47 patients with schizophrenia who were converted from ≥2 antipsychotic drugs to APM. Clinical Global Impressions and Global Assessment of Functioning scores remained unchanged, and APM was achieved in 75% of subjects with no clinical worsening. However, this study was limited by the absence of random assignment and a lack of clinical rating scales beyond the CGI; furthermore, the majority of patients were receiving first-generation antipsychotic drugs, with no patients taking clozapine, which is at odds with current patterns of antipsychotic use.[1] The second study[28] addressed a similar question in a single-blind manner involving 114 patients assigned to continue 2 antipsychotics or discontinue 1 agent as part of a design that followed individuals for 6 months. Antipsychotic monotherapy was achieved in 69% of subjects with no clinical worsening, as measured by Positive and Negative Syndrome Scale scores and improvement in side effects such as weight; however, the primary outcome measure, time to all-cause

Table 4. Comparison of Treatment Groups on Clinical Global Impressions-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) Scores (weeks 4 and 12)

	CGI-S									CGI-I	
	Worse		No Change		Improved		Total				
Group	n	%	n	%	n	%	n	%	P^a	Mean	P^b
Week 4 vs 1									.36		.52
Polypharmacy	0	0	7	43.8	9	56.3	16	100		3.60	
Monotherapy	2	13.3	7	46.7	6	40.0	15	100		3.80	
Total	2	6.5	14	45.2	15	48.4	31	100			
Week 12 vs 1									.59		.35
Polypharmacy	1	6.7	5	33.3	9	60.0	15	100		3.93	
Monotherapy	3	23.1	3	23.1	7	53.8	13	100		3.69	
Total	4	14.3	8	28.6	16	57.1	28	100			

[a]Fisher exact test. [b]Student *t* test.

medication discontinuation, indicated APP to be superior to APM. This study was limited by the absence of double-blind assignment, meaning that subjects were aware of which group they were assigned to, and allowed for a bias in this regard.

While the present study minimized such biases through a double-blind design, it is not without limitations. First, the total number of participants was relatively small (N = 35), although the study was sufficiently powered to show differences between APP and APM during the early phase of treatment. Arguably, the 12-week follow-up period used here may not be long enough to capture all of those who would deteriorate as a function of a change in their antipsychotics. For information in this regard, we turned to the aforementioned studies[27,28] that addressed this same question, both of which utilized a 6-month follow-up period. The first study[27] reported that the average time to deleterious effects was 10.3 weeks (median = 8.0 weeks), although such changes were recorded over the entire 6 months. The second investigation[28] found that, while most of the recorded medication changes (eg, in response to symptoms) occurred within 3 months, changes took place for up to 5 months. Taken together, the data support trials at least in the range of 6 months, while also agreeing that most cases involving clinical worsening will occur within the first 3 months. None of the reports, ours included, have sufficiently distinguished the role of withdrawal-related side effects in the clinical deterioration that some experience. On the point of clinical deterioration, the present investigation permitted treating physicians to increase the dose of the primary antipsychotic in such circumstances, although, in fact, they seldom did so. For the 5 cases (1 APP and 4 APM) who withdrew from the study as a result of clinical worsening, the clinicians did not choose to increase the dose. For the remaining participants who completed the study, clinicians increased the doses in 4 cases (2 APP and 2 APM) during the study period. It is not entirely clear why, but it leaves us unable to comment on whether upward dose titration of the remaining antipsychotic can effectively address clinical deterioration that may arise during a switch from APP to APM. The issue of administered medication also warrants comment. Ideally, all subjects entering the trial would be taking the same primary medication and comparable concomitant medications where required. For practical reasons, it was not possible to control for these variables; for example, by chance, 6 individuals in the monotherapy group were on depot medication versus 1 in the polypharmacy group (Table 2). Similarly, concomitant medications were not matched between groups (Table 3).

The present findings suggest that a substantial proportion of individuals with schizophrenia receiving APP can be reduced to APM safely and without clinical deterioration. Our investigation found that 77% of individuals could be successfully transitioned to APM, in line with figures of 69% and 75% reported in 2 non–double-blind studies[27,28] addressing this same question. Those who will show worsening are most likely to do so within the first 2 to 3 months, and clinicians should be particularly vigilant during this period. That said, any interpretation of these sorts of studies must take into consideration the challenges faced when balancing clinical reality against the optimal research design. Routinely, such investigations must compromise on methodological issues that include differences in primary and secondary antipsychotics, doses, concomitant medications, and other potential confounds (eg, caffeine, smoking).

Looking forward, numerous questions remain that can guide future investigations; for example, are there predictors of those who can benefit from APP or, conversely, will do worse in its absence? Interestingly, all individuals in this study who deteriorated were taking clozapine as the primary antipsychotic, raising the possibility that APP may be more effective in the so-called "ultraresistant" population ie, clozapine partial responders. Disentangling clinical deterioration from withdrawal-related side effects has received very limited attention, despite the frequency with which APP and switching occurs. Which strategies are most effective in the face of clinical deterioration (eg, reinstatement of the previous antipsychotic combination, maintaining APM with dose increments) is unclear. What is clear is that most individuals do not benefit from APP, although it appears that a minority do. Only by better defining this population are we likely to make inroads in reducing a practice that is, for most, ineffective, costly, and associated with higher antipsychotic dosing and increased side effects.[50]

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Drug names: clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol), loxapine (Adasuve), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

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