Switching to Clozapine Using Immediate Versus Gradual Antipsychotic Discontinuation: A Pilot, Double-Blind, Randomized Controlled Trial

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ABSTRACT

Objective: To examine effects of different antipsychotic discontinuation strategies on clinical outcomes in patients with schizophrenia undergoing a switch to clozapine.

Methods: This pilot, 8-week, double-blind, randomized controlled trial was conducted from May 1999 to July 2004. Outpatients with a diagnosis of schizophrenia or schizoaffective disorder based on the Structured Clinical Interview for *DSM-IV* and eligible for a switch to clozapine were included. Participants were randomly assigned to the immediate discontinuation (prior antipsychotics were discontinued at baseline) or gradual discontinuation (prior antipsychotics were reduced by 25% each week) group. For each group, clozapine was gradually increased to 300 mg/d at day 12, with this dose maintained for 3 weeks and thereafter adjusted as needed. Clinical outcome measures included the Brief Psychiatric Rating Scale (BPRS), UKU Side Effect Rating Scale, and extrapyramidal symptoms scales.

Results: Thirty-three patients were enrolled; 15 and 18 patients were assigned to the immediate and gradual discontinuation groups, respectively. While significant improvements were observed in BPRS total scores after the switch to clozapine in both groups (*P* values < .001), no significant differences were found on any clinical outcome measures between the groups; however, additional analyses revealed a significant interaction between group and time for the UKU Psychic Side Effects subscale scores (*P* = .038).

Conclusions: This preliminary study demonstrated no statistically significant differences in efficacy or tolerability between immediate and gradual antipsychotic discontinuation strategies when switching to clozapine in patients with schizophrenia; however, due to the small sample size, larger-scale trials are needed to confirm these results.

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Clozapine has been demonstrated to be clinically superior to other antipsychotics in treatment-resistant schizophrenia[1–5] and is positioned as such in treatment guidelines.[6] Because it is relegated to use in treatment-resistant schizophrenia, guidelines require that it be used only after other antipsychotics have failed[6]; accordingly, clinicians routinely contend with stopping the previous antipsychotic in making the switch to clozapine. Perhaps because of its numerous and potentially severe side effects, the issue of clozapine titration has frequently been addressed,[7–13] although to our knowledge, no study has, as of yet, assessed the comparability of immediate versus gradual antipsychotic discontinuation in switching to clozapine.

While the question has not been asked vis-à-vis clozapine, there have been several studies[14–21] examining immediate versus gradual antipsychotic discontinuation in switching antipsychotics. Immediate antipsychotic discontinuation is associated with the following risks: (1) withdrawal/discontinuation symptoms or rebound syndromes related to cholinergic, histaminergic, and serotonergic activity; (2) supersensitivity syndromes (eg, withdrawal dyskinesia, supersensitivity psychosis); and (3) exacerbation or reemergence of symptoms secondary to diminished response with the newly introduced antipsychotic.[22] On the other hand, gradual antipsychotic discontinuation is associated with the risk of worsening or emergent side effects. This said, all of the studies,[14–21] including one meta-analysis,[23] report no differences in efficacy or tolerability between immediate and gradual discontinuation strategies in antipsychotic switching. However, it should also be noted that all of the studies were conducted under an open-label design[14–16,20,21] or a single-blind design.[17–19]

To address the gap in knowledge specific to clozapine, we conducted a pilot, 8-week, double-blind, randomized controlled trial examining immediate versus gradual antipsychotic discontinuation in patients with schizophrenia undergoing a switch to clozapine. On the basis of findings from previous studies examining switching strategies to antipsychotics other than clozapine, our hypothesis was that there would be no substantial differences in efficacy or tolerability between immediate and gradual antipsychotic discontinuation when switching to clozapine.

METHODS

Study Design and Setting

This pilot study, a double-blind, parallel-group, 8-week, randomized controlled trial, was conducted at the Centre for

Clinical Points

- Clozapine is clinically superior to other antipsychotics in treatment-resistant schizophrenia. The issue of clozapine titration has frequently been addressed because of its numerous and potentially severe side effects; however, no study to date has examined immediate versus gradual antipsychotic discontinuation strategies in switching to clozapine.
- While significant improvements were observed in the BPRS total scores after the switch to clozapine in both strategies, no significant differences were found on any efficacy or tolerability measures between immediate and gradual antipsychotic discontinuation strategies.

Addiction and Mental Health (CAMH) in Toronto from May 1999 to July 2004, and the trial protocol was approved by the CAMH Research Ethics Board. After full description of the study, all participants provided written informed consent prior to trial entry. This trial was retrospectively registered at ClinicalTrials.gov (NCT02640300), because registration was not required at the time it was conducted.

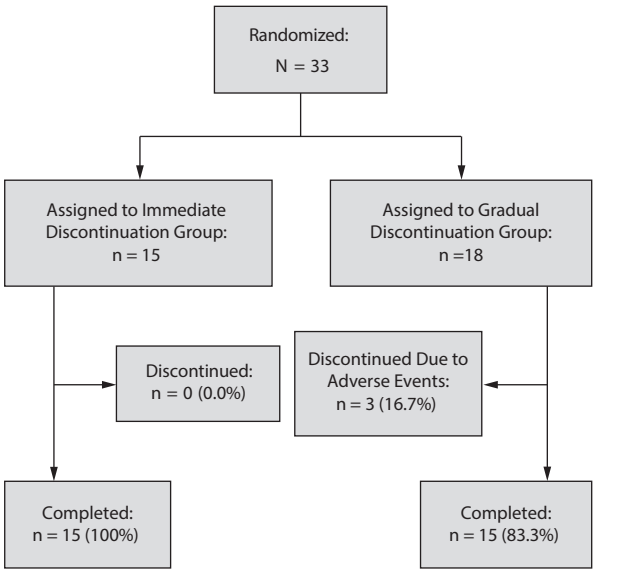
Patients

Inclusion criteria were as follows: outpatients with a diagnosis of schizophrenia or schizoaffective disorder based on the Structured Clinical Interview for *DSM-IV* (SCID-I)[24] and candidacy for a trial of clozapine, defined as an inadequate clinical response to ≥ 2 antipsychotics (detailed in a pivotal clozapine study[25]) or intolerable side effects. Exclusion criteria included: active substance use disorder; inability to undergo a trial of clozapine for medical reasons (eg, myeloproliferative disorder or history of drug-induced granulocytopenia); and evidence of significant nonadherence, defined as ≤ 75% adherence following patient interview, review of records, and discussion with treating physician and caregivers.

Procedures

Patients who met the criteria were randomly assigned to either the immediate or gradual discontinuation group. In the gradual discontinuation group, all antipsychotic drugs that patients took at baseline were changed to powder formulation and prepared in unmarked capsules, with the dose adjusted to provide a 25% reduction weekly over the next 3 weeks. If a patient received antipsychotic combination treatment, each would be administered as an unmarked capsule. The dose-tapering schedule was as follows: 3 capsules at baseline, 2 capsules at week 1, 1 capsule at week 2, and 0 capsules (ie, the antipsychotic drugs were discontinued) at week 3. For instance, if a patient had received olanzapine 20 mg/d and risperidone 4 mg/d before the study, olanzapine and risperidone were reduced to 15 mg/d and 3 mg/d at week 0, 10 mg/d and 2 mg/d at week 1, 5 mg/d and 1 mg/d at week 2, respectively, and then discontinued at week 3. In the immediate discontinuation group, all capsules contained placebo (ie, the antipsychotic drugs were abruptly discontinued). Any medications other than antipsychotic drugs that patients took were not encapsulated (ie, patients and clinicians were not blinded to those medications). For each group, clozapine was gradually increased to 300 mg/d according to the following schedule: 12.5 mg/d at day 0 and 25 mg/d increments to 300 mg/d at day 12,[26] with this dose maintained for 3 weeks, and thereafter, adjusted according to clinical judgment. Concomitant medications were kept constant throughout the study period for each group, and no rescue medications were allowed.

Figure 1. Flow of Patient Disposition



Outcome Measures

The following assessments were performed at baseline and weeks 1, 2, 3, 4, and 8: 18-item Brief Psychiatric Rating Scale (BPRS)[27] as the primary outcome measure, Clinical Global Impressions-Severity of Illness scale (CGI-S),[28] Calgary Depression Scale for Schizophrenia (CDSS),[29] Drug Attitude Inventory (DAI-10),[30] and Schedule for the Assessment of Insight (SAI)[31] for efficacy. Side effect scales included the Simpson-Angus Scale (SAS),[32] Barnes Akathisia Rating Scale (BARS),[33] Abnormal Involuntary Movement Scale (AIMS),[28] and UKU Side Effect Rating Scale (UKU).[34]

Statistical Analyses

Statistical analyses were performed on an intention-to-treat basis. Baseline demographic and clinical characteristics were compared between the 2 groups by the Fisher exact test for categorical variables and by the Student *t* test for continuous variables. Chlorpromazine equivalent antipsychotic dose was calculated according to Gardner et al.[35] The BPRS 4-factor scores (ie, reality distortion, disorganization, negative symptoms, and anxiety/depression) were calculated according to the 4-factor model established in patients with treatment-resistant schizophrenia.[36] The differences in efficacy and side effect measure scores between baseline and end point in each

Table 1. Demographic and Clinical Characteristics of Patients in Immediate and Gradual Discontinuation Groups

Characteristic	Immediate Discontinuation Group (n = 15)	Gradual Discontinuation Group (n = 18)	Group Difference, P[a]
Male, n (%)	10 (66.7)	10 (55.6)	.722
Age (y), mean (SD)	34.9 (11.3)	32.9 (11.1)	.627
Duration of illness (y), mean (SD)	10.5 (10.4)	9.4 (7.3)	.710
Pharmacologic treatment before switching to clozapine			
Dose of antipsychotics, chlorpromazine equivalent[b] (mg/d), mean (SD)	898 (486)	703 (490)	.261
Antipsychotic high-dose treatment,[c] n (%)	11 (73.3)	6 (33.3)	**.037**
Antipsychotic combination treatment, n (%)	6 (40.0)	1 (5.6)	**.030**
Type of antipsychotics, n (%)[d]			
Risperidone	0 (0.0)	3 (16.7)	
Olanzapine	4 (26.7)	8 (44.4)	
Quetiapine	3 (20.0)	3 (16.7)	
Haloperidol	0 (0.0)	1 (5.6)	
Loxapine	1 (6.7)	2 (11.1)	
Perphenazine	1 (6.7)	0 (0.0)	
Olanzapine plus risperidone	2 (13.3)	0 (0.0)	
Olanzapine plus quetiapine	2 (13.3)	0 (0.0)	
Olanzapine plus loxapine	1 (6.7)	0 (0.0)	
Olanzapine plus pimozide	1 (6.7)	0 (0.0)	
Risperidone plus trifluoperazine	0 (0.0)	1 (5.6)	
Concomitant medications, n (%)			
Anticholinergic drugs	2 (13.3)	3 (16.7)	1.000
Benzodiazepines	6 (40.0)	4 (22.2)	.448
Antidepressants	5 (33.3)	7 (38.9)	1.000
Mood stabilizers	4 (26.7)	0 (0.0)	**.033**

[a]Bold values: $P < .05$.
[b]Calculated based on the international consensus study of antipsychotic dosing.[35]
[c]Defined as chlorpromazine equivalent dose of > 600 mg/d.[37]
[d]Group difference not applicable.

group were tested by paired *t* tests using a last-observation-carried-forward (LOCF) method. The change scores from baseline to end point were compared between the 2 groups employing analysis of covariance that included baseline scores as a covariate and group as a fixed effect with a LOCF method. As an additional analysis, scores for efficacy and side effect measures over time were compared between the 2 groups employing a mixed-effects model for repeated measures (MMRM) analysis. The model included scores at each time point as a dependent variable; scores at baseline as a covariate; and group, time, and group-by-time interaction as fixed effects. A 2-tailed *P* value of < .05 was considered statistically significant for all tests. All statistical analyses were conducted using the IBM SPSS Statistics version 20 (IBM, Armonk, New York).

RESULTS

A total of 33 patients were enrolled and randomly assigned to immediate (n = 15) or gradual discontinuation (n = 18). All patients in the immediate discontinuation group completed the study, while 3 patients in the gradual discontinuation group withdrew from the study prematurely due to adverse events (Figure 1): 1 elderly patient receiving clozapine 150 mg/d, risperidone 3 mg/d, and benztropine 4 mg/d developed mild delirium at week 1; 1 on clozapine 300 mg/d and quetiapine 350 mg/d manifested marked tachycardia and hypotension at week 2; and 1 on clozapine 300 mg/d, haloperidol 5 mg/d, clonazepam 2 mg/d, and venlafaxine 125 mg/d complained about somatic concerns at week 3. This difference between the groups was statistically nonsignificant (0.0% vs 16.7%, $P = .233$, respectively).

All patients, except for 1 who withdrew from the study at week 1, received 300 mg/d of clozapine at day 12. Mean ± SD doses of clozapine at end point were 342 ± 92 mg/d and 292 ± 62 mg/d in the immediate and gradual discontinuation groups, respectively; there was no significant difference in doses at end point between the 2 groups ($P = .074$).

Patient Characteristics

Baseline demographic and clinical characteristics of the patients are shown in Table 1. The proportion of patients receiving antipsychotic combinations, high-dose treatment (defined as chlorpromazine equivalent > 600 mg/d[37]), or concomitant mood stabilizers was significantly higher in the immediate versus gradual discontinuation group. Olanzapine was prescribed as 1 of the 2 antipsychotics in 6 of the 7 patients who received antipsychotic combination treatment.

Efficacy

BPRS total, reality distortion factor, and anxiety/depression factor scores and CGI-S scores significantly improved in both the immediate and gradual discontinuation groups (Table 2). CDSS and SAI total scores significantly improved in only the gradual discontinuation group. However, there were no significant differences in changes from baseline to end point in any efficacy measure scores between the 2 groups (Table 2).

Table 2. Efficacy and Side Effect Measure Scores in Immediate and Gradual Discontinuation Groups

	Immediate Discontinuation Group (n = 15)					Gradual Discontinuation Group (n = 18)					Between-Group Difference in Change[c]
	Baseline		Change[a]		Within-Group Difference[b]	Baseline		Change[a]		Within-Group Difference[b]	
Measure	Mean	SD	Mean	SD	*P*	Mean	SD	Mean	SD	*P*	*P*
BPRS											
Total score	42.2	8.1	−8.9	5.2	**<.001**	43.7	10.9	−8.2	7.4	**<.001**	.682
Factor score[d]											
Reality distortion	16.1	4.4	−3.7	3.7	**.001**	15.7	4.0	−2.8	4.3	**.012**	.561
Disorganization	4.1	1.7	−0.5	1.2	.104	4.8	2.4	−0.4	2.3	.484	.276
Negative symptoms[e]	3.6	0.8	0.1	1.1	.634	5.8	3.7	−0.6	1.5	.145	.118
Anxiety/depression	9.1	3.3	−3.0	2.8	**.001**	8.4	3.6	−2.1	3.2	**.011**	.529
CGI-S score	4.0	0.7	−0.8	0.6	**<.001**	4.0	0.9	−0.4	0.9	**.042**	.184
CDSS total score	5.9	4.4	−2.3	4.4	.061	5.5	4.9	−1.9	3.5	**.038**	.882
DAI total score	5.3	4.1	0.8	4.6	.580	4.7	4.7	0.7	3.1	.337	.770
SAI total score	8.6	3.6	1.1	2.1	.082	10.4	3.6	0.8	1.5	**.039**	.716
SAS total score	2.1	3.2	−1.1	3.5	.228	2.5	5.4	−0.6	3.1	.479	.098
BARS total score[e]	0.5	1.2	−0.3	0.9	.173	2.3	2.7	−2.1	2.8	**.008**	.771
AIMS overall severity score	0.53	0.99	0.13	0.92	.582	0.87	1.30	−0.27	0.59	.104	.239
UKU subscale mean score[f]											
Psychic Side Effects	0.81	0.44	−0.16	0.50	.259	0.81	0.47	−0.36	0.56	**.022**	.228
Autonomic Side Effects	0.26	0.27	0.05	0.24	.407	0.23	0.19	0.06	0.22	.312	.849
Other Side Effects	0.18	0.25	−0.09	0.29	.287	0.20	0.22	−0.12	0.21	**.037**	.898

[a]Using a last-observation-carried-forward method.
[b]By paired *t* test. Bold values: $P < .05$.
[c]By analysis of covariance.
[d]Calculated based on the 4-factor model in treatment-resistant schizophrenia.[36]
[e]Significant difference in the baseline scores between the 2 groups ($P < .05$).
[f]The total score in each subscale divided by the number of the items in each subscale (ie, 10 for Psychic Side Effects, 11 for Autonomic Side Effects, 19 for Other Side Effects).
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, BPRS = Brief Psychiatric Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity of Illness scale, DAI = Drug Attitude Inventory, SAI = Schedule for the Assessment of Insight, SAS = Simpson-Angus Scale, UKU = UKU Side Effect Rating Scale.

MMRM revealed no significant interactions between group and time for any efficacy measure scores other than DAI total score ($P = .048$), indicating no significant differences in efficacy assessed by objective measurements for the 8 weeks were observed between the 2 groups. In the immediate discontinuation group, the DAI total score decreased at week 2, and thereafter, increased, while in the gradual discontinuation group, the score was generally stable over time.

Side Effects

No significant differences in changes in any side effect measure scores were observed between the 2 groups (Table 2), although BARS total and UKU Psychic Side Effects and Other Side Effects subscale mean scores significantly decreased in the gradual discontinuation group. Using MMRM, a significant interaction between group and time was found for only the UKU Psychic Side Effects subscale ($P = .038$); while the score slightly decreased over time in the immediate discontinuation group, the score in the gradual discontinuation group decreased at week 1, then increased at week 2, and thereafter decreased with a score at week 8 lower than the immediate discontinuation group.

DISCUSSION

To the best of our knowledge, this study is the first to investigate the effects of immediate versus gradual antipsychotic discontinuation on clinical outcomes in patients with schizophrenia undergoing a switch to clozapine. The findings are 2-fold: (1) a switch to clozapine improved psychopathology; and (2) generally, immediate antipsychotic discontinuation did not differ from gradual antipsychotic discontinuation in terms of efficacy or tolerability when switching to clozapine, even though a greater proportion of patients assigned to immediate antipsychotic discontinuation had received antipsychotic polypharmacy and high-dose treatment before the study. It should be noted that this was a pilot study and, as such, the sample size was small, which may contribute to some of the nonsignificant differences between the groups.

As expected, a switch to clozapine improved psychopathology in patients with treatment-resistant or treatment-intolerant schizophrenia. Prior to clozapine initiation, a majority of the patients had received atypical antipsychotic drugs such as risperidone, olanzapine, or quetiapine; approximately one-fifth of the patients had received antipsychotic polypharmacy, of which olanzapine was part of the combination in almost all cases, and approximately half of the patients received high-dose antipsychotic treatment (chlorpromazine equivalent >600 mg/d). These observations highlight once again the different strategies that are routinely tried in treatment-resistant schizophrenia prior to a trial of clozapine, while also attesting to the superiority of clozapine in treatment-resistant schizophrenia.[1–5]

Several explanations might account for the absence of significant differences in efficacy and tolerability between immediate and gradual antipsychotic discontinuation during a switch to clozapine—one being clozapine's

unique pharmacologic profile. Clozapine and its active metabolite (ie, norclozapine) bind to a diverse range of neurotransmitter receptors including dopaminergic, serotoninergic, histaminergic, noradrenergic, and muscarinic.[38] This multireceptor binding profile, including clozapine's antagonistic action on the cholinergic system,[38] may mitigate against the risk of withdrawal symptoms, in particular cholinergic rebound in the case of antipsychotics with high anticholinergic activity.[22] Notably, two-thirds of patients in the immediate discontinuation group were taking olanzapine before a switch to clozapine. On the other hand, differences in changes over time were observed between immediate and gradual antipsychotic discontinuation for patient attitude toward medication and mental side effects; the former and latter outcomes at week 2 were favorable for gradual and immediate antipsychotic discontinuation, respectively. These findings suggest that clinicians can choose either strategy based on clinical judgment when conducting a switch to clozapine.

A second and quite plausible explanation is that differences do not exist between switching strategies, regardless of what antipsychotic the individual is being switched to. This was the finding of a previous meta-analysis examining other antipsychotics,[23] and the present results are consistent with studies in which patients were exposed to similar switching strategies while being moved to antipsychotic drugs including risperidone,[18] olanzapine,[14,15] ziprasidone,[17,20] aripiprazole,[16,19] and iloperidone.[21] In these studies, patients were administered a wide range of antipsychotics prior to the antipsychotic switch, including haloperidol[14,15,20] and other typical antipsychotics,[14,17,20] risperidone,[14,16,17,19,21] olanzapine,[16–19,21] and aripiprazole.[21] Regardless of prior or newly introduced antipsychotic, it would appear that immediate discontinuation of the former is not different from gradual discontinuation on measures of efficacy or tolerability.

Limitations of the present study warrant comment. First, there is a risk of type II errors because of the small sample size. Second, the follow-up period of 8 weeks may be too short to assess adverse consequences of antipsychotic switching strategies, but the duration of this study is comparable to or longer than most studies examining antipsychotic switching strategies.[14–18,20] Finally, results may have been influenced by other psychotropic medications, in particular benzodiazepines and mood stabilizers, which were prescribed in the immediate discontinuation group more than the gradual discontinuation group; however, these medications were kept constant throughout the study.

In conclusion, and as has been demonstrated repeatedly,[1–5] a switch to clozapine improved psychopathology in patients with treatment-resistant schizophrenia. We also demonstrated that in switching to clozapine, immediate discontinuation of the prior antipsychotic was, in general, not significantly different with respect to efficacy or tolerability from overlapping treatment and gradual discontinuation, a strategy we believe is used much more frequently in clinical practice, although differences were observed in the course of patient attitude toward medication and mental side effects between the 2 strategies. Our results from this pilot study, specific to clozapine, must be viewed as preliminary and should be confirmed in further larger-scale trials, although we once again highlight that the present findings align with evidence specific to various other antipsychotics.

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Drug names: aripiprazole (Abilify), clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), iloperidone (Fanapt), loxapine (Loxitane and others), olanzapine (Zyprexa and others), pimozide (Orap), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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