An Algorithm-Based Approach to First-Episode Schizophrenia: Response Rates Over 3 Prospective Antipsychotic Trials With a Retrospective Data Analysis

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ABSTRACT

Objective: Early, effective treatment in first-episode schizophrenia is advocated, although evidence based on a systematic approach over multiple antipsychotic trials is lacking. Employing a naturalistic design, we examined response rates over 3 circumscribed antipsychotic trials.

Method: Between June 2003 and December 2008, 244 individuals with first-episode schizophrenia or schizoaffective disorder according to *DSM-IV* criteria were treated at the Centre for Addiction and Mental Health, Toronto, Ontario, Canada, following an algorithm that moved them through 2 antipsychotic trials, followed by a trial with clozapine. For the first 2 trials, treatment consisted of risperidone followed by olanzapine, or vice versa; each trial consisted of 3 stages (low-, full-, or high-dose) lasting up to 4 weeks at each level and adjusted according to response/tolerability. Clinical response was defined as a Clinical Global Impressions-Improvement score of 2 (much improved) or 1 (very much improved) and/or a Brief Psychiatric Rating Scale Thought Disorder subscale score ≤ 6. Data were analyzed retrospectively, and publication of anonymized clinical data was approved by the Research Ethics Board of the Centre for Addiction and Mental Health in May 2003.

Results: In trial 1, 74.5% of individuals responded, with rates significantly higher for olanzapine (82.1%, 115/140) versus risperidone (66.3%, 69/104; $P = .005$). With trial 2, response rate dropped dramatically to 16.6% but again was significantly higher for olanzapine (25.7%, 9/35) compared to risperidone (4.0%, 1/25; $P = .04$). Response rate climbed above 70% once more, specifically 75.0% (21/28), in those individuals who agreed to a third trial with clozapine.

Conclusions: Results confirm a high response rate (75%) to initial antipsychotic treatment in first-episode schizophrenia. A considerably lower response rate (< 20%) occurs with a second antipsychotic trial. Results here were specific to olanzapine and risperidone, suggesting clinical differences (ie, olanzapine more effective than risperidone). A subsequent trial with clozapine is clearly warranted, although it remains unclear whether outcome would be further enhanced if it were used earlier in the treatment algorithm.

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Various guidelines for the management of schizophrenia have been published that also include antipsychotic treatment algorithms, as a rule derived through expert opinion and consensus.[1–9] While there may be debate in the field around selected topics (eg, the superiority of newer versus conventional antipsychotics), the face validity of these guidelines has been reinforced by their general agreement regarding the recommendation of several antipsychotic trials followed by clozapine in the case of treatment resistance.

However, studies examining the outcome of trials using these algorithms are lacking, particularly with respect to the systematic evaluation of individuals across antipsychotic trials from the onset of treatment in first-episode psychosis. It is unclear, for example, as to response rates following antipsychotic switching in individuals with first-episode schizophrenia who fail to achieve adequate response to their initial antipsychotic trial. Specifically, how many of these individuals respond to a second antipsychotic in the face of an adequate (ie, dose, duration) first trial that produces suboptimal results? More recent information has called into question the value of switching antipsychotics,[10,11] although it has rightfully been pointed out that these data are not reflective of switching early in the course of treatment.[12] Along similar lines, according to most algorithms clozapine is relegated to third-line treatment,[1–9] but how effective is it in individuals who have had only 2 failed antipsychotic trials? Its clinical superiority has been clearly established in the more chronic refractory population,[13] but these are individuals who have often been ill for many years and have been exposed to numerous antipsychotic trials. Conversely, clozapine has not proven superior in first-episode schizophrenia,[14,15] perhaps related to the very high response rate in this population with any antipsychotic.

The present study addresses the issue of antipsychotic switching in first-episode schizophrenia, examining response rates as individuals are moved through antipsychotic trials. It bears both the advantages and disadvantages of real-world, naturalistic investigations, but in this context it offers an opportunity to evaluate a large cohort of first-episode patients who are systematically treated from the outset of their illness, including a potential trial with clozapine following 2 failed antipsychotic trials. To the authors' knowledge, this is the first such investigation reporting on a dataset addressing the aforementioned questions in such a population.

METHOD

Patients

Patients were referred to the First-Episode Psychosis Program at the Centre for Addiction and Mental Health, Toronto, Ontario, Canada, between June 2003 and December 2008. A treatment

algorithm standardizing pharmacologic management was implemented, in keeping with existing guidelines.[1–9] Second-generation antipsychotics (SGAs) were identified as the treatment of choice, and during this period those approved for clinical use in Canada included risperidone, olanzapine, quetiapine, and clozapine.

Patients were advised that their treatment would be applied according to this algorithm but that it would be flexibly administered in accordance with the individual's specific clinical condition and preferences. An initial analysis (N = 123), focused on those who received clozapine, has been published previously.[16] The Research Ethics Board (REB) of the Centre for Addiction and Mental Health approved this study. Because data for this study were collected in the course of routine clinical care, and these data were analyzed retrospectively, informed consent was neither sought nor obtained. However, approval from the REB chair for publication of anonymized clinical data was sought and obtained at the time standardized assessments were adopted in May 2003.

Assessments

A *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) diagnosis was made through clinical interview by a staff psychiatrist (O.A.) who oversaw the care and assessment of this cohort during treatment. All patients met criteria for schizophrenia or schizoaffective disorder, and for the purpose of reporting are referred to collectively as having first-episode schizophrenia. Clinical ratings included the Clinical Global Impressions scale (CGI)[17] and the 18-item Brief Psychiatric Rating Scale (BPRS),[18] administered weekly during the first month, then monthly thereafter. Response to treatment was defined as (a) CGI-I score = 2 (much improved) or 1 (very much improved) and/or (b) BPRS Thought Disorder subscale (conceptual disorganization; hallucinatory behavior; suspiciousness; unusual thought content) score ≤ 6.

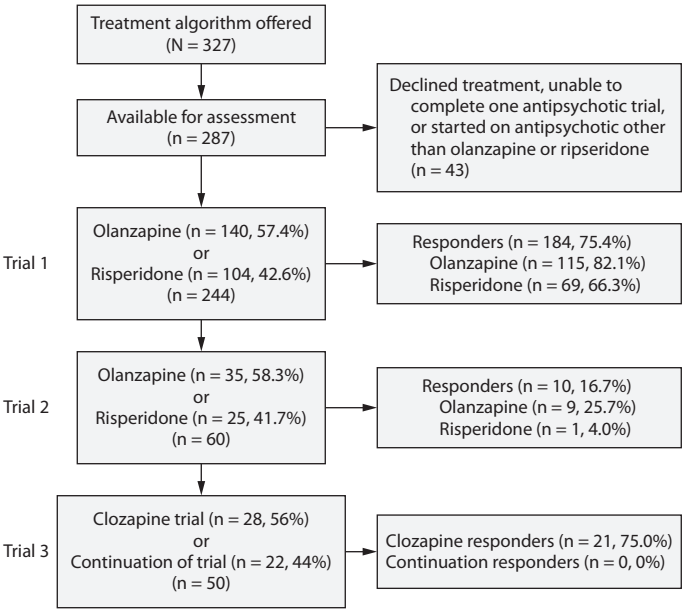
Treatment Algorithm

Patients were offered trials with 2 SGAs, excepting clozapine. Each antipsychotic trial was divided into 3 stages based on dose, and each stage could last for a maximum of 4 weeks. If the patient failed to meet criteria for response at this point, he or she was advanced to the next stage of treatment. The treating psychiatrist could also increase the dose before the 4-week assessment if clinically indicated.

The 3 dosing stages for each trial were established as follows (dose adjustment within range as clinically indicated/tolerated): low-dose (olanzapine, 5–10 mg; risperidone, 2–3 mg; quetiapine, 300–400 mg daily); full-dose (olanzapine, 12.5–20 mg; risperidone, 4–6 mg; quetiapine, 425–800 mg daily); and high-dose (olanzapine, 22.5–30 mg; risperidone, 6.5–10 mg; quetiapine, 850–1200 mg daily).

If, after 2 trials, response criteria were not met, a trial of clozapine was offered. Clozapine was started at 12.5 mg/d and titrated upward daily in 25-mg increments, as tolerated.

Figure 1. Outcome for Treatment Algorithm in Patients (N = 327) With *DSM-IV* First-Episode Schizophrenia or Schizoaffective Disorder



Abbreviation: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.

Table 1. Sociodemographic and Clinical Characteristics of Patients (N = 244) With First-Episode *DSM-IV* Schizophrenia or Schizoaffective Disorder

Characteristic	Value
Age, y	
Mean (SD)	22.2 (4.4)
Range	16–38
Sex, n (%)	
Male	181 (74.2)
Female	63 (25.8)
Ethnicity, n (%)	
White	122 (50)
Other	122 (50)
Country of birth, n (%)	
Canada	138 (56.6)
Other	106 (43.4)
Education, mean (SD), y	9.6 (2.2)
Diagnosis, n (%)	
Schizophrenia	189 (77.5)
Schizoaffective disorder	55 (22.5)

Abbreviation: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.

Medication adherence was assessed through a combination of approaches, including patient and caregiver feedback, as well as random pill counts. For the data presented here, evidence from pill counts indicated an adherence rate ≥ 80%.

Statistics

Comparative rates of response were assessed using Fisher exact test, 2-tailed. Odds ratios were calculated to assess the relevance of preselected variables and response, with χ^2 values reported to evaluate significance. In the case of specific

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Table 2. Antipsychotic, Response Rate, and Dosing for 3 Antipsychotic Trials in Patients With First-Episode *DSM-IV* Schizophrenia or Schizoaffective Disorder

Variable	Trial 1	Trial 2	Trial 3
Subjects, n	244	60	28
Receiving olanzapine, n	140	35	NA
Receiving risperidone, n	104	25	NA
Response to olanzapine, n (%)	115 (82.1)	9 (25.7)	NA
Response to risperidone, n (%)	69 (66.3)	1 (4.0)	NA
Overall response, n (%)	184 (75.4)	10 (16.6)	21 (75.0)
Olanzapine dose at time of response, mean (SD), mg/d	15.8 (3.7)	15.3 (3.2)	NA
Risperidone dose at time of response, mean (SD), mg/d	4.3 (1.1)	3.0	NA
Switched to olanzapine, n	35	24	NA
Risperidone dose at switch, mean (SD), mg/d	6.8 (4.4)	6.6 (0.2)	NA
Switched to risperidone, n	25	26	NA
Olanzapine dose at switch, mean (SD), mg/d	27.5 (2.2)	27.2 (2.1)	NA
Clozapine dose at time of response, mean (SD), mg/d	NA	NA	385.7 (91.4)

Abbreviations: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; NA = not applicable.

Table 3. Association Between Selected Characteristics of Patients With First-Episode *DSM-IV* Schizophrenia or Schizoaffective Disorder and First-Line Treatment Response

Characteristic	n	Responders, n (%)	OR	95% CI	χ^2	*df*	*P*
Antipsychotic							
Olanzapine (n = 140)	140	115 (82.1)	2.33	1.29–4.23	7.82	1	.0052
Risperidone (n = 104)	104	69 (66.3)	1	…			
Sex				…	0.028		.87
Male	181	136 (75.1)	1				
Female	63	48 (76.2)	1.06	0.54–2.07			
Country of birth				…	1.39	1	.24
Canada	138	108 (78.3)	1				
Other	106	76 (71.7)	0.70	0.39–1.26			
Ethnicity				…	4.62	4	.33
White	122	92 (75.4)	1				
African	42	35 (83.3)	1.63	0.66–4.05			
West Asian	34	22 (64.7)	0.60	0.27–1.35			
East/Southeast Asian	35	28 (80.0)	1.30	0.52–3.29			
Other	11	7 (63.6)	0.57	0.16–2.09			
Hospitalization[a]			1.11	0.60–2.07	0.12	1	.73
Yes	167	127 (76.1)					
No	77	57 (74.0)	1	…			

[a]Hospitalization recorded during time frame of trials.
Abbreviations: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; OR = odds ratio.

antipsychotic (olanzapine versus risperidone), a corrected risk ratio was also determined.[19] To examine whether there was value in going to high doses in Trial 1, as well as the utility of a second antipsychotic trial before clozapine, an exact test of significance, 1-tailed, was employed in each case.

RESULTS

A trial following this algorithm was offered to 327 patients, with 287 individuals available for assessment (Figure 1). Of this group, 32 (11.1%) declined treatment or were unable to complete the first antipsychotic trial. Thus, a total of 255 individuals reached that point following treatment with the first antipsychotic at which they met criteria for response or were offered a second antipsychotic trial due to suboptimal response.

Of note, 95.7% (N = 244) of patients in first antipsychotic trials received either olanzapine or risperidone (olanzapine, 54.5%; risperidone, 41.2%), with quetiapine prescribed to the remaining 11 patients (4.3%). This allocation is in line with clinician preference regarding choice of antipsychotic over the longer term in our setting, in which olanzapine and risperidone continue to predominate.

Given that almost all individuals were treated with olanzapine and risperidone in the first 2 antipsychotic trials, response rates being reported here are confined to these individuals. Thus, the data being presented speak to a population that has received either olanzapine followed by risperidone, or vice versa, over the first 2 antipsychotic trials.

The makeup of this sample (N = 244) very much mirrors what we observe in the real-world clinical practice of our specialized First-Episode Psychosis Program: it is largely male (74.2%), young (mean age = 22.2 years), and ethnoculturally diverse (reflecting the population of Toronto), with *DSM-IV* schizophrenia (77.5%) the predominant diagnosis (Table 1).

Trial 1

Olanzapine was used more frequently as first-line treatment, 57.4% (n = 140) versus 42.6% (n = 104) for risperidone. A total of 184 patients (75.4%) met criteria for response, with rates significantly higher for those who received olanzapine (olanzapine 82.1%, n = 115; risperidone 66.3%, n = 69, $P = .005$, 2-tailed). Mean ± SD dose at the time of achieving response was 15.8 ± 3.7 mg for olanzapine (range, 7.5–30 mg) and 4.3 mg ± 1.1 mg for risperidone (range, 2.5–7.0 mg; Table 2). Of note, 71% of individuals responded to the first 2 dosing stages, which incorporated the routine therapeutic range for these drugs (ie, olanzapine, 5–20 mg; or risperidone, 2–6 mg daily).

Table 3 shows the distribution of first-line treatment responders across a number of preselected variables of interest. Of note, antipsychotic dose was not included here, as not all individuals were exposed to each dose. The only variable significantly associated with first-line treatment response was antipsychotic treatment, with a corrected risk ratio of 1.2 (95% CI, 1.08–1.35).[19]

Table 4 shows the clinical status of the responders to trials 1–3 at start and end of each trial.

Trial 2

Patients who did not respond to a first SGA trial (24.6%, n = 60) were subsequently switched to a second SGA. As

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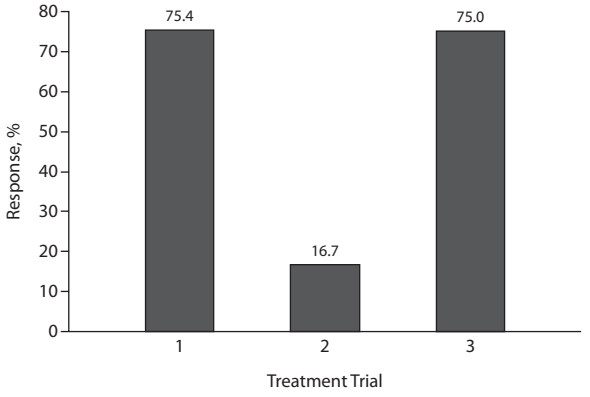
Table 4. Clinical Status of Responders With First-Episode *DSM-IV* Schizophrenia or Schizoaffective Disorder at Start and End of Each Antipsychotic Trial

Responders (n)	Outcome Measure	Baseline Score, Mean ((SD)	End Point Score, Mean (SD)	Difference in Mean Scores	Statistical Significance
Trial 1 (184)	CGI-S score	5.3 (0.8)	1.9 (0.6)	3.3	Wilcoxon signed rank test: $P < .0001$
	BPRS-Psychosis score	18.2 (2.7)	5.8 (1.4)	12.4	$t_{183} = 51.5$, $P < .0001$
	BPRS total score	57.2 (4.6)	25.0 (5.5)	32.2	$t_{183} = 59.9$, $P < .0001$
Trial 2 (10)	CGI-S score	5.2 (1.0)	2.1 (0.3)	3.1	Wilcoxon signed rank test: $P = .0020$
	BPRS-Psychosis score	16.1 (1.3)	5.7 (2.2)	10.4	$t_9 = 11.4$, $P < .0001$
	BPRS total score	53.6 (3.5)	25.4 (7.2)	28.2	$t_9 = 11.7$, $P < .0001$
Trial 3 (21)	CGI-S score	4.9 (0.5)	2.4 (0.6)	2.5	Wilcoxon signed rank test: $P < .0001$
	BPRS-Psychosis score	16.0 (1.9)	6.0 (1.4)	10.0	$t_{20} = 16.3$, $P < .0001$
	BPRS total score	54.2 (4.1)	25.9 (5.0)	28.3	$t_{20} = 19.5$, $P < .0001$

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.

Figure 2. Response Rates for Antipsychotic Trials 1 and 2 (olanzapine or risperidone) Followed by Trial 3 (clozapine)



noted, in this sample those demonstrating a suboptimal response to olanzapine were moved to risperidone or vice versa. For this trial, however, response rate was notably lower, decreasing from the 75.4% rate in Trial 1 to 16.6% (n = 10). Again though, response rate was significantly higher for those receiving olanzapine (25.7%, 9/35 risperidone nonresponders) as compared to risperidone (4.0%, 1/25 olanzapine nonresponders; $P = .04$, 2-tailed). For those responding to olanzapine in Trial 2, the mean ± SD daily dose was 15.3 ± 3.2 mg (range, 10–20 mg), and for the 1 patient responding to risperidone, the mean daily dose was 3.0 mg.

Trial 3

Of the remaining 50 individuals, 56% (n = 28) agreed to a trial of clozapine. Response rate here was 75.0% (n = 21), approximating the rate established for Trial 1 and sharply contrasting with the drop to less than 20% observed in Trial 2 (Figure 2). Those responding to clozapine did so within 12 weeks and at a mean ± SD daily dose of 385.7 ± 91.4 mg (range, 250–600 mg). Individuals who declined clozapine were not switched to a third SGA during this time interval but continued receiving the SGA initiated during Trial 2, either risperidone or olanzapine. None converted to responder status during this same time period.

DISCUSSION

To our knowledge, this is the first naturalistic investigation reported that follows individuals with first-episode schizophrenia through 2 systematic SGA trials, followed thereafter by a trial of clozapine in those continuing to demonstrate suboptimal response. This algorithm follows current guidelines for best clinical practice, suggesting several antipsychotic trials followed by clozapine in the case of treatment resistance,[1–9] and in doing so it offers an excellent opportunity to assess patterns of response in the illness' earliest stages. The present finding of a 75% response rate to the first antipsychotic trial is in keeping with previous investigations that have reported a high response rate in first-episode schizophrenia.[20,21]

In contrast, it is striking that only 16.6% of those who went on to a second antipsychotic trial met criteria for response, although 75% of the nonresponders who agreed to take clozapine as a trial subsequently responded, despite 2 trials with other SGAs. Clozapine produced a marked and significant improvement, whereas those who were not switched to clozapine in a third antipsychotic trial were continued on their existing antipsychotic therapy, without benefit. These findings speak to clozapine's unique superiority, even among the newer antipsychotics, in treating individuals who prove refractory to standard treatment, and they are in line with other reports that have confirmed this response in more chronic populations.[22–26]

The design of the algorithm employed here does not address a number of important clinical issues. We have provided data on only 2 SGAs, olanzapine and risperidone, in trials leading up to clozapine, and it remains to be seen whether other SGAs would provide comparable results. There are data suggesting that the newer antipsychotics may vary in terms of both efficacy and side effect profile.[27–30]

On this topic, our own results found olanzapine superior to risperidone, and while this finding is in line with those of the recently published CATIE trial,[31] which involved a more chronic population, our results must be viewed tentatively given the naturalistic design of this study.[27] Moreover, our results are at odds with those of 2 controlled trials involving these same agents in early schizophrenia, although

both represented longer trials on each medication (ie, 4–12 months with each treatment).[32,33] First-generation antipsychotics (FGAs) were not employed at any point in this algorithm, so no data are available to tell us whether systematic trials with FGAs would produce similar findings. We are, however, reminded that existing evidence establishing the superiority of SGAs over FGAs, including in this population, is equivocal at best.

The present data are also not positioned to answer the question of whether clozapine might prove even more effective if it were offered earlier in the course of treatment. Current evidence does not support clozapine's superiority when employed as first-line treatment,[14,15] possibly reflecting the already high response rate that is observed with other antipsychotics in this group. Given clozapine's side effect profile and need for hematologic monitoring, it is unlikely that individuals would even choose it as first-line treatment when such a high response rate can be attained with other agents. Indeed, the response rate of other antipsychotics used as second-line treatment (16.6%) may also lead patients to choose another agent even if clozapine were available at this point. Be that as it may, our results cannot answer whether the efficacy of clozapine would be improved further if individuals were offered it earlier in treatment (ie, as second-line treatment). In addition, the present investigation does not provide information on the value of a third nonclozapine antipsychotic trial. It does seem unlikely that a third trial with another SGA would produce a treatment response higher than the 16.6% noted for the second trial, but this possibility cannot be ruled out. It is hard to imagine that a third trial with another SGA would achieve the level of response reported for clozapine here (ie, 75%) but this question must be confirmed, and we are presently examining the question, offering those who reach Stage 3 another SGA trial should they decline clozapine at this point.

Various other limitations related to the study's design warrant comment. The data are drawn from a busy clinical program, making blinding untenable. Outcome measures, again based on practical issues, were limited, and the present data are confined to shorter term response rates focused on clinical versus functional response. Objective measures, such as plasma levels and urine screens, to assess potential confounds (eg, nonadherence, substance abuse) were not systematically employed. A single psychiatrist was responsible for all ratings, an arrangement that can be seen as both an advantage (ie, circumventing issues of interrater reliability) and a disadvantage (ie, personal biases in a nonblinded setting).

Notwithstanding these limitations, the findings very much represent real-world clinical practice. The population here is sizable, and it represents first-episode individuals with a *DSM-IV* diagnosis of schizophrenia or schizoaffective disorder seen in the context of an academic, community-based specialty program. A detailed, well-circumscribed treatment algorithm was implemented to ensure adequate antipsychotic trials and a systematic approach to patient care. Decisions reflecting antipsychotic choice, dosing, and trial duration reflect the consensus of various academic psychiatrists and current best practice guidelines. The findings do not meet the standards of more rigorous, controlled efficacy studies, but they are in line with the increasing interest in, and demand for, evidence that better reflects actual clinical practice.[33] As more recent studies of this sort have demonstrated, results are not always aligned with the more rigorous efficacy-type investigations.[29, 34,35]

In summary, the present findings confirm that response is high initially in first-episode schizophrenia or schizoaffective disorder, but decreases markedly (ie, to less than 20%) in the subgroup that fails to respond effectively to a first antipsychotic trial. Clozapine, even as a third-line treatment, appears capable of establishing a response rate more in line with that observed with initial treatment. Taken together, these results underscore the importance of moving individuals through treatment and to clozapine in a timely and systematic fashion. It is unlikely at this time that this type of work will be corroborated with FGAs—the current standards of care, justified or not, generally recommend SGAs over FGAs in first-episode schizophrenia. However, whether clozapine may prove more useful as a second-line treatment seems an important and viable question.

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