Introduction

Evaluating Clinical Trial Data From Schizophrenia Research

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Clinical research trials are vital to the effective and safe use of new drugs. When conducted competently and analyzed correctly, clinical trials yield valuable information that will ultimately be disseminated to and interpreted by physicians in clinical practice. Therefore, it is important to understand the issues raised and the questions answered by clinical trials. To that end, a group of distinguished researchers held a symposium to discuss the issues influencing clinical trial data: hypotheses and hypothesis testing, patient selection and dropout rates, study design, outcome measures, dose selection and comparator drugs, statistical analyses, and interpretations and conclusions. Data from 5 recent clinical trials comparing atypical antipsychotics were presented in each segment to explain by example the issue under discussion (Table 1).[1–5]

The Tran et al. study[1] compared the efficacy and safety of olanzapine versus risperidone in 339 subjects with schizophrenia, schizophreniform disorder, and schizoaffective disorder. The 28-week study was published in 1997 and was sponsored by Eli Lilly and Company. Conley, Mahmoud, et al.[2] compared the efficacy and safety of risperidone versus olanzapine in 407 subjects with diagnoses of schizophrenia or schizoaffective disorder. The 8-week study was presented in poster format in 1999 and was sponsored by Janssen Pharmaceutica. The QUEST trial[3] compared efficacy and tolerability of medication in 751 subjects who were randomly assigned in a 3:1 ratio to either quetiapine or risperidone. The diagnostic criteria of the QUEST study were quite broad, and a majority of the sample did not have a diagnosis of schizophrenia. The trial, which lasted 4 months, was also presented in poster format in 1999 and was sponsored by Zeneca Pharmaceuticals. The Ho et al. study[4] was a 6-month effectiveness study that focused on symptom reduction, extrapyramidal side effects, and quality of life in 42 schizophrenic patients taking either risperidone or olanzapine. The study was published in 1999 and was sponsored by the National Institute of Mental Health and the University of Iowa. The Conley et al. study[5] analyzed 1-year rehospitalization rates in 372 newly discharged schizophrenic patients who were taking either atypical antipsychotics (risperidone, olanzapine, or clozapine) or conventional depot antipsychotics (haloperidol or fluphenazine decanoate). The study was presented in poster format in 1999 and was sponsored by the Maryland Psychiatric Research Center at the University of Maryland.

Atypical antipsychotics are now the recommended first-line treatment for patients with schizophrenia, but there are few data to guide the selection of a particular atypical agent. This Supplement demonstrates the importance of understanding the methodology of a clinical trial because differences in methodology can make comparisons challenging.

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Table 1. Data From 5 Recent Comparisons of Atypical Antipsychotics[a]

Characteristic	Tran et al[1]	Conley, Mahmoud, et al[2]	QUEST[3]	Ho et al[4]	Conley et al[5]
Hypothesis/aim	Compare safety, efficacy of RIS vs OLZ	Compare safety, efficacy of RIS vs OLZ	Compare tolerability, efficacy of QUE vs RIS	Compare relative effectiveness of RIS vs OLZ	Compare rehospitalization rates of CLZ, RIS, OLZ, vs HAL or FLU decanoate
Patient sample	339 in/outpatients; DSM-IV schizophrenia, schizophreniform or schizoaffective disorders; BPRS score ≥ 42	407 in/outpatients; DSM-IV schizophrenia, schizoaffective disorder; PANSS score ≥ 60 and ≤ 120	751 outpatients; DSM-IV psychotic disorders	42 in/outpatients; DSM-IV schizophrenia	372 newly discharged patients; schizophrenia
Dropout rates, %	RIS, 52.7 OLZ, 42.4	RIS, 28 OLZ, 23	Unknown	RIS, 50 OLZ, 50	Unknown
Study design	28 wk, RCT, double-blind, prospective	8 wk, RCT, double-blind, prospective	4 mo, open; randomly assigned in 3:1 ratio to QUE:RIS	6 mo, open	1 y, prospective
Outcome measures	PANSS, BPRS, CGI, SANS, Simpson-Angus, Barnes Akathisia, AIMS, Quality of Life	PANSS, ESRS, body weight, BMI	EPS checklist, CGI, PANSS, HAM-D, DAI-10	SANS, SAPS, BPRS, GAS, Simpson-Angus, Barnes Akathisia, Quality of Life	1 y rehospitalization rates; mean number of d in community
Mean dose, mg/d	RIS, 7.2 OLZ, 17.2	RIS, 4.8 OLZ, 12.4	RIS, 4.4 QUE, 253.9	RIS, 5.7 (6 wk) RIS, 4.5 (5.2 mo) OLZ, 14.4 (6 wk) OLZ, 13.8 (5.2 mo)	RIS, 4.8 OLZ, 16.3 CLZ, 430.7 HAL 181.5 mg/mo FLU 46.1 mg q 2 wk
Statistical analysis	1-tailed t test	2-tailed t test	Unknown	2-tailed t test	Unknown
Conclusion	OLZ = RIS safety, efficacy; OLZ > RIS on SANS, PANSS total; RIS > OLZ adverse effects, EPS; OLZ > RIS weight gain	RIS = OLZ safety, efficacy; RIS > OLZ improved positive symptoms (8 wk); RIS = OLZ EPS; OLZ > RIS weight gain, BMI	QUE > RIS for depression; QUE = RIS on PANSS; QUE < RIS EPS events	RIS = OLZ as acute treatment; RIS > OLZ for psychotic symptoms at 6 mo; RIS = OLZ inducing parkinsonism; RIS > OLZ inducing akathisia	Readmission rates lower for atypical than depot drugs

[a]Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, CLZ = clozapine, DAI-10 = Drug Attitude Inventory, EPS = extrapyramidal symptoms, ESRS = Extrapyramidal Symptom Rating Scale, FLU = fluphenazine decanoate, GAS = Global Assessment Scale, HAL = haloperidol decanoate, HAM-D = Hamilton Rating Scale for Depression, OLZ = olanzapine, PANSS = Positive and Negative Syndrome Scale, QUE = quetiapine, RCT = randomized controlled trial, RIS = risperidone, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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