HHS Public Access

Author manuscript

Am J Psychiatry. Author manuscript; available in PMC 2015 March 13.

Published in final edited form as:

Am J Psychiatry. 2015 March 1; 172(3): 237–248. doi:10.1176/appi.ajp.2014.13101355.

Medication Prescription Practices for the Treatment of First Episode Schizophrenia-Spectrum Disorders: Data from the National RAISE-ETP Study

Delbert G. Robinson, M.D.[1,2,3], **Nina R. Schooler, Ph.D.**[4], **Majnu John, Ph.D.**[1,3], **Christoph U. Correll, M.D.**[1,2,3,5], **Patricia Marcy, BSN**[3], **Jean Addington, Ph.D**[6], **Mary F. Brunette, M.D.**[7,8], **Sue E. Estroff, Ph.D.**[9,11], **Kim T. Mueser, Ph.D.**[10], **David Penn, Ph.D.**[11], **James Robinson, M.Ed.**[12,13], **Robert A. Rosenheck, M.D.**[14], **Joanne Severe, M.S.**[15], **Amy Goldstein, Ph.D.**[15], **Susan Azrin, Ph.D.**[15], **Robert Heinssen, Ph.D.**[15], and **John M. Kane, M.D.**[1,2,3,5]

[1]The Feinstein Institute for Medical Research, Center for Psychiatric Neuroscience, Manhasset, NY, USA

[2]Hofstra North Shore-LIJ School of Medicine, Departments of Psychiatry and of Molecular Medicine, Hempstead, NY, USA

[3]The Zucker Hillside Hospital, Psychiatry Research, North Shore-Long Island Jewish Health System, Glen Oaks, NY, USA

[4]SUNY Downstate Medical Center, NY, USA

[5]Albert Einstein College of Medicine, Bronx, NY, USA

[6]Hotchkiss Brain Institute Department of Psychiatry University of Calgary, Calgary, Canada

Corresponding author: Delbert Robinson, M.D., Research Department, The Zucker Hillside Hospital, 75-59 263rd Street, Glen Oaks, New York 11004; drobinso@nshs.edu.

Previous presentation: Partial study findings were presented at the New Clinical Drug Evaluation Unit (NCDEU) 52nd Annual Meeting held May 28 to 31st, 2013 in Hollywood, Florida and at the American Psychiatric Association 167th Annual Meeting held May 3 to 7, 2014 in New York, New York.

Location of work: From the Feinstein Institute for Medical Research, Manhasset, New York and the Departments of Psychiatry and of Molecular Medicine, Hofstra North Shore LIJ School of Medicine, Hempstead, New York.

Disclosures: Dr. D. Robinson has been a consultant to Asubio and Shire, and he has received grants from Bristol Meyers Squibb, Janssen, and Otsuka.
Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Actelion, Alexza; American Academy of Child and Adolescent Psychiatry, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, GersonLehrman Group, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, National Institute of Mental Health, Janssen/J&J, Otsuka, Pfizer, ProPhase, Roche, Sunovion, Takeda, Teva, and Vanda. He has received grant support from BMS, Feinstein Institute for Medical Research, Janssen/J&J, National Institute of Mental Health (NIMH), National Alliance for Research in Schizophrenia and Depression (NARSAD), and Otsuka. Dr. Schooler has been a consultant to Abbott, AMGEN, Eli Lilly, Janssen Psychiatry, Lundbeck, Merck, Nupathe. Pfizer, and Shire, and she has received grants from Astra Zeneca, Bristol Meyers Squibb, Eli Lilly, H. Lundbeck, OrthoMcNeil Janssen, Neurocrine, Otsuka, and Pfizer. Ms. Marcy is a shareholder of Pfizer. Dr. Addington has served as a consultant to Roche. Dr. Rosenheck has received research support from Janssen Pharmaceutica, and Wyeth Pharmaceuticals. He has been a consultant to Otsuka. He provided expert testimony for the plaintiffs in UFCW Local 1776 and Participating Employers Health and Welfare Fund, et al. v. Eli Lilly and Company; for the respondent in Eli Lilly Canada Inc vs Novapharm Ltd and Minister of Health; for the Patent Medicines Prices Review Board Canada, in the matter of Janssen Ortho Inc. and “Risperdal Consta”, and was testifying expert in Jones ex rel. the State of Texas v. Janssen Phamaceutica et al. Dr. Kane has been a consultant and/or advisor to or has received honoraria from: Alkermes, Amgen, Bristol-Myers Squibb, Eli Lilly, Esai, Forrest Labs, Genentech, Gerson Lehman Group, IntraCellular Therapies, Janssen, Jazz, J & J, Lundbeck, MedAvante, Merck, Novartis, Otsuka, Pierre Fabre, Proteus, Pfizer, Roche, Reviva, Sunovion, Takeda, Targacept, Vanda. He is a shareholder of MedAvante.
Drs. John, Brunette, Mueser, Estroff, Penn, Azrin, Goldstein and Heinssen have nothing to disclose nor do Ms. Severe or Mr. Robinson.

[7]Geisel School of Medicine at Dartmouth, Dartmouth, NH, USA

[8]Bureau of Behavioral Health, CHHS, Dartmouth, NH, USA

[9]Department of Social Medicine, University of North Carolina, Chapel Hill, NC, USA

[10]Center for Psychiatric Rehabilitation, Departments of Occupational Therapy, Psychiatry, and Psychology, Boston University, Boston, MA, USA

[11]Department of Psychology, University of North Carolina, Chapel Hill, NC, USA

[12]Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA

[13]New York University Langone Medical Center, Department of Psychiatry & Adolescent and Child Psychiatry, New York, NY, USA

[14]Yale School of Medicine, Departments of Psychiatry and Epidemiology and Public Health, New Haven, CT, USA

[15]National Institute of Mental Health, Bethesda, MD, USA

Abstract

Objective—Treatment guidelines suggest distinctive medication strategies for first episode and multi-episode patients with schizophrenia. How much community clinicians adjust their usual treatment regimens for first episode patients is unknown. We examined prescription patterns and factors associated with prescription choice within a national cohort of early phase patients.

Method—Study entry prescription data (before any influence on treatment by study procedures) were obtained from 404 participants in the RAISE-ETP study, a US nationwide effectiveness study conducted at 34 community treatment centers in 21 states for patients with first episode schizophrenia-spectrum disorders. Subjects had been treated with antipsychotics for 6 months or less at study entry.

Results—We identified 159 subjects (39.4% of the sample) who might benefit from changes in their psychotropic prescriptions. Of these 159 subjects, 8.8% were prescribed recommended antipsychotics at higher than recommended doses, 32.1% were prescribed olanzapine (often at high doses), 23.3% more than one antipsychotic, 36.5% an antipsychotic but also an antidepressant without a clear indication, 10.1% psychotropic medications without an antipsychotic and 1.2% stimulants.

Multivariate analyses found evidence for sex, age and insurance status effects on medication prescription. Racial and ethnic effects consistent with effects found in prior multi-episode studies were found in univariate analyses. There were some regional variation in prescription practices; when present, regional patterns varied across prescribing practices. Diagnosis had limited, and inconsistent, effects.

Conclusions—Besides prescriber education, policy makers may need to consider not only patient factors but also service delivery factors in efforts to improve first episode prescription practices.

Clinical Trials registration—NCT01321177: An Integrated Program for the Treatment of First Episode of Psychosis (RAISE ETP), http://www.clinicaltrials.gov/ct2/show/NCT01321177

Introduction

Research supports different medication treatment approaches for first episode and multi-episode schizophrenia (reviewed (1)) and recent schizophrenia treatment practice guidelines (e.g (2–6)) include specific first episode recommendations. Since the incidence of schizophrenia is low (7), most clinicians' experience outside of specialty centers is heavily weighted towards the treatment of multi-episode patients. How much community clinicians adjust their treatment regimens for first episode patients is unknown.

The Early Treatment Program (ETP) study, a nationwide comparative effectiveness trial that is part of the National Institute of Mental Health *Recovery After an Initial Schizophrenia Episode* (RAISE) initiative, provided the basis for the first national report of U.S. community mental health center medication treatments for the crucial early phase of schizophrenia. We addressed two questions: what are the medication treatments currently used in community settings and are there factors associated with choice of medication strategies.

Method

Study overview

RAISE-ETP compares NAVIGATE, a coordinated specialty care treatment program for first episode psychosis that includes medical management guided by a decision support system, individual therapy, family psychoeducation, and supported employment and education, and Community Care, treatment determined by clinician choice. RAISE-ETP was conducted under the guidance of the respective institutional review boards for the coordinating center and the sites.

The design prioritized enhancing generalizability of findings to community settings. Inclusion/exclusion criteria were chosen to allow broad inclusion of different patient subgroups. Inclusion criteria were: age 15 to 40 years; diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis NOS or brief psychotic disorder; beginning first treatment for psychosis (defined as having taken antipsychotic medications cumulatively for 6 months or less) and ability to participate in research assessments in English. Exclusion criteria were: had clearly experienced more than one discrete psychotic episode; diagnosis of bipolar disorder, psychotic depression, substance-induced psychotic disorder or current psychotic disorder due to a general medical condition; presence of current neurological disorders that would affect diagnosis or prognosis; clinically significant head trauma or other serious medical conditions that would significantly impair assessment, functioning or treatment. All subjects provided written informed consent (or written assent for those under age 18 along with parent's/guardian's written consent).

We employed site randomization to facilitate participation by sites without previous research experience, to eliminate potential treatment strategy "spillover" effects and to enhance study acceptability by patients who would not need to agree to individual randomization. Thirty-four sites in 21 states were selected after a national search. All were community treatment

centers with no preexisting first episode program. Sites were intentionally located in diverse settings, ranging from large urban to rural settings. Seventeen sites were randomized to deliver NAVIGATE treatment and 17 to Community Care.

RAISE-ETP data specific to this report were collected between July 2010 and July 2012.

RAISE-ETP assessments pertinent to this report: Site staff obtained medication data using all available sources of information including direct interview with subjects and their families (if available) and record review. Medication history collection was a priority in order to establish study eligibility that specified maximum antipsychotic treatment duration. We present data on psychotropic medications being prescribed (even if not actually taken) to subjects at study entry and before any influence on treatment by study guidelines or procedures. Diagnoses were determined using the Structured Clinical Interview for Axis 1 DSM-IV Disorders Patient Edition (SCID) (8) administered by masked remote assessors via live, two-way video. Information sources were the subjects and a structured summary of subject symptoms and treatment history provided to the assessor prior to the SCID interview. Tobacco smoking status was assessed with the Fagerstrom (9) questionnaire. Data about recent alcohol and substance use was obtained by clinic staff using record review and direct interview of patients and their families (if available).

Statistical analyses

Prescribing patterns were characterized using standard descriptive methods (e.g. percentages). Potential correlates for the analyses of prescribing patterns were chosen based on the following. Sex (10), racial background (11–13) and ethnicity (14) influence antipsychotic response or prescription patterns with multi-episode patients. Cigarette smoking decreases blood levels of some psychotropics (15). Age was included because some agents have adolescent indications. Prior depressive or anxiety symptoms should influence antidepressant prescription. Prescription may differ among the various schizophrenia-spectrum disorders or by the presence of concurrent substance use. Insurance status influences access to particular medications and also treatment settings in the U.S. Our data from 21 states allowed us to examine regional variations in prescription. We examined these factors in relation to nine key prescription practices: antipsychotic prescription, prescription of more than one antipsychotic, long acting injectable antipsychotic prescription, first generation antipsychotic prescription, risperidone prescription and dose, olanzapine prescription and dose and antidepressant prescription.

We adopted a Bayesian perspective for the correlates analyses. As an aid to readers unfamiliar with Bayesian analyses, we review some features of Bayesian analyses. Bayesian analyses do not require correction for multiple comparisons (16). Bayesian credible intervals (CrIs) are similar to confidence intervals (CI) in classical analyses, but in the Bayesian framework, the interval contains the true population parameter. Bayesian analyses do not generate p-values. Instead, the posterior probability of being a risk factor (PPRF), also sometimes referred to as selected %, is the probability that a variable is associated with an outcome. The larger the PPRF, the stronger the evidence for an association. We present PPRF evidence classifications adapted from (17,18): <50% lacking evidence, 50–75% some evidence, 75–95% positive evidence, 95–99% strong evidence and >99% very strong

evidence for an association with outcomes. Studies (18) comparing results from classical and Bayesian analyses provide additional context for PPRF interpretation. These studies show that variables that are not significant in classical analyses have Bayesian PPRFs of less (often much less) than 50%.

For all analyses, a weakly informative prior distribution was constructed by first scaling all non-binary variables to have mean 0 and standard deviation 0.5, and then placing an independent distribution from the Student *t* prior family (specifically, a Cauchy distribution centered at zero and 2.5 scale) on the coefficients (19). This prior has the advantage of always giving solutions even when there is complete separation in the logistic regression (20,21). Univariate analysis was done using the *bayesglm* function in the *arm* package in R; *sim* function was used to obtain simulates of the posterior distribution of each coefficient in the general linear model, and 95% Crls were obtained based on the 2.5^{th} and 97.5^{th} percentiles of the posterior distribution. Multivariate analyses employed Bayesian model averaging (BMA), a Bayesian solution to the problem of inference in the presence of multiple competing models (18). The *bic.glm* function from R package *BMA* was primarily used for these analyses.

Results

Subjects

The CONSORT diagram Supplemental Figure 1 presents the enrollment flow. The sample included 404 subjects. Community centers normally do not do outreach; new patients arrive through referral from inpatient units, other clinicians or self-referral. This pattern mostly held for the study; 335 (83%) subjects came from these sources and only 88 (17%) from outreach activities (e.g. educating the professional community about RAISE-ETP; educational efforts with potential patients and their families through articles in the local press, information booths at community events). As shown in Table 1, most subjects had a psychiatric hospitalization before study entry. Subjects were mostly young, male and from diverse racial backgrounds. Approximately half met DSM-IV criteria for schizophrenia; the next most common diagnoses were schizophreniform disorder and schizoaffective disorder. Consistent with early phase illness, mean cumulative lifetime antipsychotic treatment was only 46.7 (95% CI: 42.2, 51.2) days.

The frequency of prescription of major medication classes is presented in Table 2

Most subjects were prescribed antipsychotics and approximately a third of subjects were prescribed antidepressants.

Subjects not prescribed antipsychotic medications at study entry

All subjects had a psychotic disorder for which antipsychotic treatment is indicated. Fifty-one (12.6%) subjects were not prescribed any psychotropic medications at study entry. Twenty-four (47.1%) of these had had a psychiatric inpatient admission and 16 (31.4%) had taken antipsychotics in the past. Sixteen subjects were prescribed psychotropic medications but not antipsychotics. Fourteen of these were prescribed antidepressants, 1 clonazepam and 1 clonidine.

Antipsychotic prescribing patterns

Of the 337 subjects prescribed an antipsychotic, only 40 (11.9%) were prescribed a first generation agent, including subjects prescribed both a first and a second generation antipsychotic. Long acting injectable antipsychotics were prescribed for 32 (9.5%) of the 337 subjects who were prescribed antipsychotics. Frequency of long acting injectable prescription was: paliperidone palmitate 17 (53.1% of long acting prescriptions); 11 (34.4%) haloperidol decanoate; 3 (9.4%) risperidone microspheres and 1 (3.1%) for fluphenazine decanoate.

Antipsychotic monotherapy was by far the most common pattern. Three hundred (89.0%) of the 337 subjects prescribed antipsychotics were prescribed only one antipsychotic (either in single or multiple formulations), 35 (10.4%) were prescribed 2 different antipsychotics and 2 (0.6%) were prescribed 3 different antipsychotics.

Prescriptions for antipsychotic monotherapy—As shown in Table 3, risperidone accounted for approximately one-third of the 300 prescriptions for antipsychotic monotherapy. The next most commonly prescribed antipsychotic was olanzapine (17.0% of prescriptions) followed by aripiprazole, paliperidone and quetiapine each accounting for around 10% of prescriptions.

First episode schizophrenia treatment guidelines emphasize using low-dose strategies. As shown in Table 3, relatively few subjects were prescribed antipsychotic doses higher than the suggested 2009 PORT (4) upper dosing limit for multi-episode patients. High dose strategies were found for only certain medications, notably olanzapine. 44.9% of olanzapine prescriptions were above specific 2009 PORT guidelines (4) for first episode treatment compared with only 7.8% of risperidone prescriptions.

Prescriptions for two or more antipsychotics—Prescriptions for multiple antipsychotics included combinations of 13 different antipsychotics. The most commonly prescribed agents were: risperidone prescribed to 16 (43.2%) of the 37 subjects prescribed multiple agents; quetiapine prescribed to 13 (35.1%) subjects; olanzapine prescribed to 10 (27.0%); aripiprazole to 9 (24.3%) and haloperidol to 8 (21.6%).

Medications for motor side effects—We lack data on perceived indications for prescriptions but anti-cholinergic medications and beta blockers are usually prescribed for motor side effects in patients taking antipsychotics. 71 (21.1%) of the 337 subjects prescribed an antipsychotic were concurrently prescribed an anti-cholinergic medication and 7 (2.1%) a beta blocker. Anti-anxiety agents can be prescribed for motor side effects and/or for anxiety. Thirty-nine (11.6%) of the 337 were prescribed an anti-anxiety agent.

Antidepressants prescribed with antipsychotics—One hundred fifteen subjects were prescribed both an antidepressant and an antipsychotic. Only 57 (49.6%) of the 115 had any SCID interview documentation of lifetime depression (i.e. major depression, depressive disorder NOS, schizoaffective disorder, depressive type) or anxiety (i.e. panic disorder, social phobias, obsessive-compulsive disorder, post traumatic stress disorder, generalized anxiety disorder, anxiety due to a medical condition, anxiety disorder NOS) that

might broadly be considered justification for antidepressant treatment. Although not recommended by treatment guidelines, antidepressants are sometimes prescribed for negative symptoms. However, only 6 (10.3%) of the remaining 58 subjects prescribed antidepressants had any prominent negative symptoms by SCID interview.

Factors associated with prescribing patterns

These analyses are summarized in main text Figure 1 and 2 and presented in detail in Supplemental Materials Tables 1 and 2. *Antipsychotic prescription*. Univariate but not multivariate analyses (all PPRFs <21.2%; all lacking evidence) suggested that women and subjects with public versus private insurance were less likely to receive an antipsychotic while those with schizophreniform versus schizophrenia or schizoaffective disorder were more likely to receive an antipsychotic prescription. *Prescriptions for two or more antipsychotics* were more likely for subjects at southern versus Midwestern sites in univariate but not multivariate analyses (PPRF=4.6%; lacking evidence). In multivariate analyses subjects with private insurance were less likely to be prescribed more than one antipsychotic than either subjects with public (PPRF=52.9%; some evidence) or no insurance (PPRF=51.9%; some evidence). *Long acting injectable prescription* was more frequent for women and subjects at Midwestern versus western sites based upon univariate but not multivariate analyses (PPRF=40.2% and 20.9%, respectively; both lacking evidence). *First generation antipsychotic prescription.* Multivariate analyses showed that first generation antipsychotic prescription was more common among the uninsured versus those with private (PPRF=96.2%; strong evidence) or public insurance (PPRF=56.4%; some evidence); African Americans were more likely than Caucasians to be prescribed first generation antipsychotics based upon univariate but not multivariate analyses (PPRF=23.1%; lacking evidence). *Risperidone prescription.* Multivariate analyses revealed that younger subjects (PPRF=66.4%; some evidence) and univariate analyses only that Hispanics (PPRF=17.5%; lacking evidence) and other racial groups (PPRF=17.5%; lacking evidence) versus Caucasians were more likely to be prescribed risperidone. *Risperidone dose.* Women received lower risperidone doses than men (PPRF=52.2%; some evidence). Univarite but not multivariate analyses (all PPRFs <17%; all lacking evidence) showed that subjects with psychosis NOS or schizoaffective disorder versus those with schizophrenia as well as those with public versus no insurance were prescribed lower risperidone doses. *Olanzapine prescription i*n univariate but not multivariate analyses (all PPRFs <24%; all lacking evidence) was more likely among subjects at western versus southern sites and among those with schizophrenifrom disorder versus psychosis NOS or schizophrenia. *Olanzapine dose* was lower among women than men and for those with schizoaffective disorder versus psychosis NOS based upon univariate but not multivariate analyses (PPRFs=47.7% and 9.7%, respectively; all lacking evidence). *Antidepressant prescription* was more likely among women (PPRF=83.5%; positive evidence) and those with depression or anxiety symptoms (PPRF=87.1%; positive evidence); older subjects and those with schizoaffective disorder versus psychosis NOS were more likely to receive antidepressants based upon univariate analyses only (PPRF=23.8% and 1.6%, respectively; all lacking evidence).

Subjects who might benefit from prescription modifications

These analyses excluded subjects not being prescribed psychotropic medications at baseline as some would not be expected to have prescriptions (e.g. someone initiating psychiatric treatment at study entry). One hundred fifty-nine subjects (39.4% of the entire sample) met criterion for potential benefit. Of these, 14 (8.8%) were prescribed recommended antipsychotics at higher than recommended doses, 51 (32.1%) were prescribed olanzapine (often at high doses), 37 (23.3%) more than one antipsychotic, 58 (36.5%) an antipsychotic but also an antidepressant without a clear indication, 16 (10.1%) psychotropic medications without an antipsychotic and 5 (1.2%) stimulants.

Discussion

This is the first report of psychotropic medication treatment of people with first episode schizophrenia-spectrum disorders in US community mental health settings. The Tiihonon national Finnish discharge registery study (22) provides an international comparison. Both studies found similar prescription rates for long acting injectables and for multiple antipsychotics. Risperidone followed by olanzapine were the most commonly used oral antipsychotics in both countries. Clozapine use was much higher in Finland. This may reflect different treatment practices or the possibility that more of the Finnish subjects failed to respond to other antipsychotics during outpatient treatment before cohort identification based upon their first hospitalization.

Practice guidelines (e.g. (2–6)) with specific first-episode recommendations and first-episode research data support 1) the need for antipsychotic treatment, 2) using low antipsychotic dosing and 3) the need to minimize side effects, especially metabolic ones, during early phase treatment. Did community clinicians follow these core principles? The need for antipsychotic treatment was widely recognized. Only 16 subjects were not being prescribed antipsychotics who clearly had been evaluated for psychiatric problems as evidenced by the prescription for a psychotropic agent. Another 35 subjects were not prescribed any psychotropics; how many had recently seen a prescriber who did not recognize a need for psychotropic agents is unknown. Antipsychotic prescriptions were mostly concordant with recommendations. An exception was the relatively common use (17.0% of antipsychotic prescriptions) of olanzapine. Due to its more frequent adverse metabolic side effects (23), especially with first-episode patients (24), PORT guidelines recommend that olanzapine not be used for first-episode treatment. Strikingly, olanzapine compared with other antipsychotics was much more frequently prescribed at higher than recommended doses. We considered the possibility that olanzapine was prescribed for subjects who had not improved with other antipsychotics but the data do not support this. The mean days of antipsychotic treatment for subjects prescribed olanzapine (56.2 (95% CI: 45.7, 66.7)) was similar to that for other antipsychotics (e.g. 57.8 (95% CI: 44.3, 71.3) for paliperidone). Regarding minimizing side effects, this requires optimizing all medications, not just antipsychotics. Of note, antidepressants were prescribed for around a third of subjects but only around half of these subjects had clear symptom indications for antidepressants.

Our univariate analyses identified specific factors associated with particular prescription practices. Prescription maybe influenced by several factors. People designing practice improvement efforts may wish to focus upon factors identified by the multivariate analyses due to these being less biased when confounding factors are present. Both analysis types are informative in different contexts and we include both in our discussion. Demographic: As with multi-episode subjects (10), women in our sample received lower antipsychotic doses. They were also more likely to be prescribed a long acting injectable antipsychotic (univariate only) and, even controlling for depressive and anxiety symptoms, an antidepressant. In multi-episode studies African Americans are more likely to be prescribed a first generation antipsychotic (12,13) and Hispanics risperidone (25); our univariate results suggest that these patterns may also apply to first-episode treatment. Younger subjects were more likely to be prescribed risperidone, possibly because of its FDA adolescent treatment indication. Service delivery: We found some univariate regional differences in prescription practices; the regions that differed varied across prescription practices with no region consistently having different practices from the other regions. Insurance status effects were highly consistent. Private insurance was associated with better medication prescription: increased likelihood of antipsychotic prescription and less likelihood of receiving 2 or more antipsychotics or receiving a first generation antipsychotic, a medication choice discouraged by some (e.g. (3)) but not all (e.g. (4)) first-episode guidelines. Diagnosis: Diagnosis had no effect on prescription of more than 1 antipsychotic or prescription of long acting injectables, first generation antipsychotics or risperidone. The univariate association between schizoaffective diagnoses and antidepressant prescription is consistent with the mood symptoms required for the diagnosis; the basis for the univariate association between schizophreniform disorder and olanzapine prescription is unclear. Diagnostic associations were not consistent across analyses of risperidone and olanzapine dosing. Smoking and substance use was not associated with risperidone or olanzapine dosing.

Our data have limitations. Our sample may not be as generalizable as a true epidemiological sample despite being recruited from 34 sites in 21 states. Second, most subjects' prescriptions were made at another facility, usually an inpatient unit, prior to referral to our study community centers. Thus, we lack data on the prescribing clinicians' decision processes, their perceived indications for prescriptions and of the effects of patient preferences. Third, our sample's mean total lifetime antipsychotic prescription was only 46.7 days. For most subjects, past treatment response should not have substantially influenced medication selection but some subjects may have had enough treatment to document unusual responses to medication leading to treatment not conforming to guidelines. Fourth, our large number of sites prevented including individual sites in our analyses. Grouping sites into geographic regions provided a means to examine uniformity of prescribing patterns nationally, but cannot provide data on individual site practices.

Despite these limitations, our data have health policy implications. The marked use of second over first generation antipsychotics in our study may be warranted by evidence of better efficacy (26) and relapse prevention (27) and less motor side effects (26) with second generation antipsychotics with early phase patients. However, the marked metabolic effects of some second generation antipsychotics with early phase patients (28–32) suggests that

efforts (e.g. (33)) to increase adherence with recommended physical health monitoring of first-episode patients should be strongly encouraged.

Although each questionable medication practice we identified affected only between 1.2% to 14.4% of subjects, cumulatively 39.4% of subjects might have benefited from psychotropic prescriptions changes. Primary immediate targets for improving first-episode community treatment are discouraging use of two or more antipsychotics and the prescription of, and high dose of, olanzapine. Besides educational efforts to prescribers, changes in reimbursement models or care delivery may need to be considered to facilitate evidence-based treatment during the crucial early phase of schizophrenia. Subjects with private insurance had strikingly lower rates of prescription of two or more antipsychotics than patients with public or no insurance.

A large number of our subjects received antidepressants without clear indications for their use. Either prescribers responded to symptoms not detected by our research interviews or they interpreted schizophrenia symptoms as mood or anxiety symptoms. If the latter is true, training to improve clinicians' ability to diagnose schizophrenia-spectrum disorders as distinct from mood or anxiety disorders in women would be warranted given our finding that women were more likely to be prescribed antidepressants independent of symptom indications.

Better medication treatment of the initial illness episode raises the possibility of better acute and long-term outcomes. An important first-episode research question is whether promoting more evidence-based care does indeed improve outcomes and, if it does, what level of adherence to evidence-based practice is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We wish to thank the participating patients and their families. We also wish to acknowledge the contributions of the staff at our 34 sites: Burrell Behavioral Health (Columbia), Burrell Behavioral Health (Springfield), Catholic Social Services of Washtenaw County, Center for Rural and Community Behavior Health New Mexico, Cherry Street Health Services, Clinton-Eaton-Ingham Community Mental Health Authority, Cobb County Community Services Board, Community Alternatives, Community Mental Health Center of Lancaster County, Community Mental Health Center, Inc., Eyerly Ball Iowa, Grady Health Systems, Henderson Mental Health Center, Howard Center, Human Development Center, Lehigh Valley Hospital, Life Management Center of Northwest Florida, Mental Health Center of Denver, Mental Health Center of Greater Manchester, Nashua Mental Health, North Point Health and Wellness, Park Center, PeaceHealth Oregon/Lane County Behavioral Health Services, Pine Belt Mental HC, River Parish Mental Health Center, Providence Center, San Fernando Mental Health Center, Santa Clarita Mental Health Center, South Shore Mental Health Center, St. Clare's Hospital, Staten Island University Hospital, Terrebonne Mental Health Center, United Services and University of Missouri-Kansas City School of Pharmacy.

Funding for the RAISE-ETP study was provided by the National Institute of Mental Health (NIMH), Bethesda, MD (HHSN-271-2009-00019C; PI: Dr. Kane). Additional support for these analyses was provided by an ACISR award (P30MH090590; PI: Dr. Kane) also from NIMH.

References

1. Robinson DG, Woerner MG, Delman HC, Kane JM. Pharmacological treatments for first-episode schizophrenia. Schizophr Bull. 2005; 31(3):705. [PubMed: 16006592]
2. Clinical practice guidelines. Treatment of schizophrenia. Can J Psychiatry Rev Can Psychiatr. 2005 Nov; 50(13 Suppl 1):7S–57S.
3. Moore TA, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, Essock SM, Finnerty M, Marder SR, Miller DD, McEvoy JP, Robinson DG, Schooler NS, Shon SP, Stroup TS, Miller AL. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry. 2007; 68(11):1751–62. [PubMed: 18052569]
4. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Himelhoch S, Fang B, Peterson E, Aquino PR, Keller W. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010; 36(1):71–93. [PubMed: 19955390]
5. Barnes TRE. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol Oxf Engl. 2011 May; 25(5):567–620.
6. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Thibaut F, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry. 2013 Feb; 14(1):2–44. [PubMed: 23216388]
7. McGrath J, Saha S, Welham J, Saadi OE, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med. 2004 Apr 28.2(1):13. [PubMed: 15115547]
8. First, M.; Spitzer, R.; Gibbon, M.; Williams, J. Structured Clinical Interview for Axis 1 DSM-IV Disorders Patient Edition. New York: Biometrics Research, New York State Psychiatric Institute; 1998.
9. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict. 1991 Sep; 86(9): 1119–27. [PubMed: 1932883]
10. Seeman MV. Gender differences in the prescribing of antipsychotic drugs. Am J Psychiatry. 2004 Aug; 161(8):1324–33. [PubMed: 15285956]
11. Kuno E, Rothbard AB. Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. Am J Psychiatry. 2002 Apr; 159(4):567–72. [PubMed: 11925294]
12. Daumit GL, Crum RM, Guallar E, Powe NR, Primm AB, Steinwachs DM, Ford DE. Outpatient prescriptions for atypical antipsychotics for African Americans, Hispanics, and whites in the United States. Arch Gen Psychiatry. 2003; 60(2):121. [PubMed: 12578429]
13. Herbeck DM, West JC, Ruditis I, Duffy FF, Fitek DJ, Bell CC, Snowden LR. Variations in use of second-generation antipsychotic medication by race among adult psychiatric patients. Psychiatr Serv. 2004; 55(6):677–84. [PubMed: 15175466]
14. Busch AB, Lehman AF, Goldman H, Frank RG. Changes over time and disparities in schizophrenia treatment quality. Med Care. 2009 Feb; 47(2):199–207. [PubMed: 19169121]
15. Desai HD, Seabolt J, Jann DMW. Smoking in patients receiving psychotropic medications. CNS Drugs. 2001 Jun 1; 15(6):469–94. [PubMed: 11524025]
16. Gelman A, Hill J, Yajima M. Why we (usually) don't have to worry about multiple comparisons. J Res Educ Eff. 2012; 5(2):189–211.
17. Kass RE, Raftery AE. Bayes factors. J Am Stat Assoc. 1995; 90(430):773–95.
18. Viallefont V, Raftery AE, Richardson S. Variable selection and Bayesian model averaging in case-control studies. Stat Med. 2001; 20(21):3215–30. [PubMed: 11746314]
19. Gelman A, Jakulin A, Pittau MG, Su Y-S. A weakly informative default prior distribution for logistic and other regression models. Ann Appl Stat. 2008:1360–83.

20. Albert A, Anderson JA. On the existence of maximum likelihood estimates in logistic regression models. Biometrika. 1984; 71(1):1–10.
21. Lesaffre E, Albert A. Partial separation in logistic discrimination. J R Stat Soc Ser B Methodol. 1989; 51(1):109–16.
22. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011 Jun 1; 168(6):603–9. [PubMed: 21362741]
23. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2012 Feb; 8(2):114–26. [PubMed: 22009159]
24. Foley DL, Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Arch Gen Psychiatry. 2011 Jun; 68(6):609–16. [PubMed: 21300937]
25. Ren XS, Kazis LE, Lee AF, Huang Y-H, Hamed A, Cunningham F, Herz L, Miller DR. Patient characteristics and the likelihood of initiation on olanzapine or risperidone among patients with schizophrenia. Schizophr Res. 2005 Sep 15; 77(2–3):167–77. [PubMed: 15894460]
26. Zhang J-P, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol Off Sci J Coll Int Neuropsychopharmacol CINP. 2012 Dec 3.:1–14.
27. Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey PD, Kopala L, McGorry PD, Van Hove I, Eerdekens M, Swyzen W, De Smedt G. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry. 2005 May; 162(5):947–53. [PubMed: 15863797]
28. Lieberman JA, Tollefson G, Tohen M, Green AI, Gur RE, Kahn R, McEvoy J, Perkins D, Sharma T, Zipursky R, Wei H, Hamer RM. HGDH Study Group. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psychiatry. 2003; 160(8):1396. [PubMed: 12900300]
29. Robinson DG, Woerner MG, Napolitano B, Patel RC, Sevy SM, Gunduz-Bruce H, Soto-Perello JM, Mendelowitz A, Khadivi A, Miller R, McCormack J, Lorell BS, Lesser ML, Schooler NS, Kane JM. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes. Am J Psychiatry. 2006 Dec; 163(12):2096–102. [PubMed: 17151160]
30. McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, Sweitzer D, Olexy C, Weiden P, Strakowski SD. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry. 2007; 164(7):1050. [PubMed: 17606657]
31. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, López-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rössler A, Grobbee DE. EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. The Lancet. 2008 Mar 29; 371(9618):1085–97.
32. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. JAMA J Am Med Assoc. 2009; 302(16):1765–73.
33. Thompson A, Hetrick SE, Alvarez-Jiménez M, Parker AG, Willet M, Hughes F, Gariup M, Gomez DL, McGorry PD. Targeted intervention to improve monitoring of antipsychotic-induced weight gain and metabolic disturbance in first episode psychosis. Aust N Z J Psychiatry. 2011 Sep; 45(9): 740–8. [PubMed: 21827345]

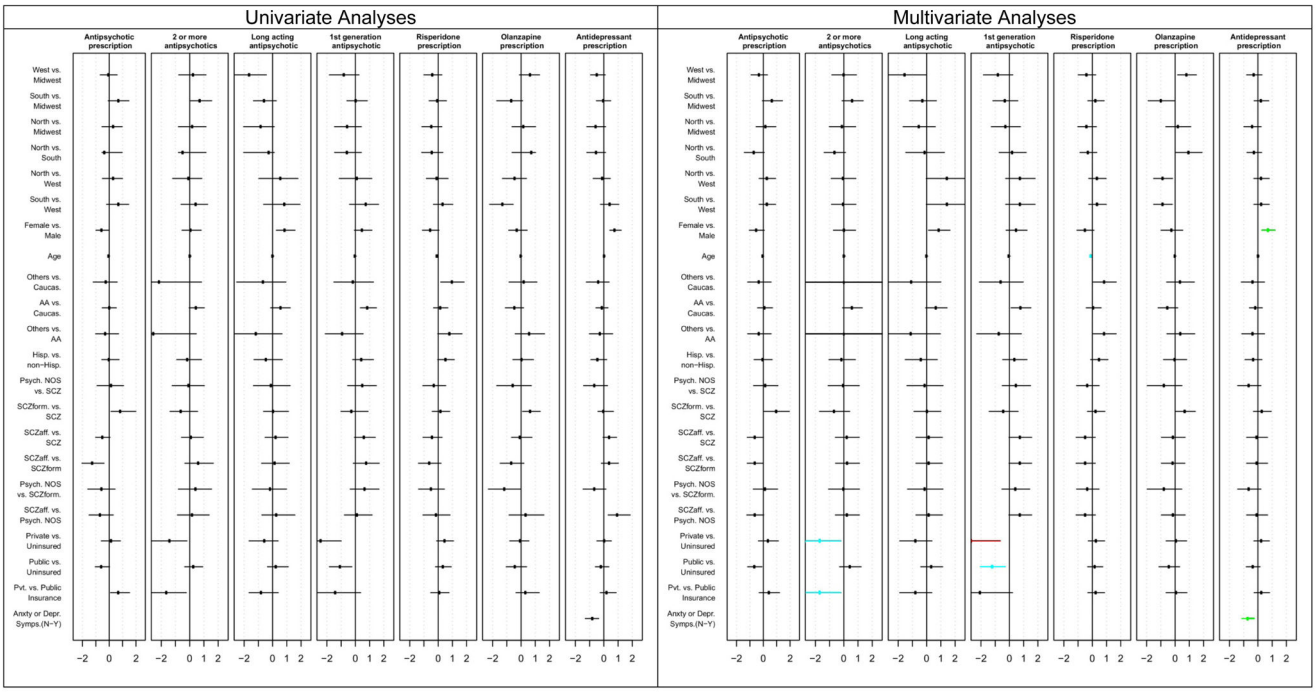

Figure 1. Factors Associated with Prescription Patterns Log Odds Ratios and 95% Credible Intervals

Odds ratios in aqua are from multivariate analyses with selected % of 50% or greater but less than 75% (some evidence of association)

Odds ratios in green are from multivariate analyses with selected % of 75% or greater but less than 95% (positive evidence of association)

Odds ratios in red are from multivariate analyses with selected % of 95% or greater but less than 99% (strong evidence of association)

Antipsychotic prescription = prescription of one or more antipsychotics versus no antipsychotic prescribed

2 or more antipsychotics = prescription for 2 or more antipsychotics among subjects prescribed antipsychotics. Multiple formulations of the same antipsychotic were counted as a single antipsychotic.

Long acting antipsychotic = prescription for long acting antipsychotic or a long acting antipsychotic plus an oral antipsychotic among subjects prescribed antipsychotics

1st generation antipsychotic = prescription for a first generation antipsychotic or both a first and second generation antipsychotic among subjects prescribed antipsychotics

Risperidone prescription = prescription for risperidone among subjects prescribed only 1 antipsychotic. Multiple formulations of the same antipsychotic were counted as a single antipsychotic.

Olanzapine prescription = prescription for olanzapine among subjects prescribed only 1 antipsychotic. Multiple formulations of the same antipsychotic were counted as a single antipsychotic.

Antidepressant prescription = prescription for one or more antidepressants.

Caucas = Caucasian

Others = racial categories other than Caucasian and African-American

AA = African-American
Hisp = Hispanic
Non-Hisp. = not of Hispanic ethnicity
Psych. NOS = psychosis NOS
SCZ = schizophrenia
SCZform = schizophreniform
SCzaff = schizoaffective disorder
Pvt = private
Anxty or Depr. Symps (N-Y) = presence of anxiety or depressive symptoms (not present versus present)

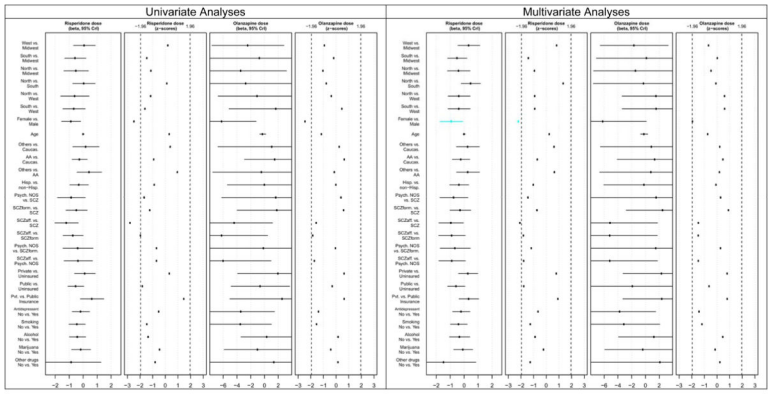

Figure 2. Factors Associated with Dosing Patterns For Oral Risperidone or Olanzapine Beta and Z Scores and 95% Credible Intervals

Dosing data (expressed as total daily dose) are from prescriptions requiring patients to take a single antipsychotic solely in an oral formulation

Doses in aqua are from multivariate analyses with selected % of 50% or greater but less than 75% (some evidence of association)

CrI = Credible Interval

Caucas = Caucasian

Others = racial categories other than Caucasian and African-American

AA = African-American

Hisp = Hispanic

Non-Hisp. = not of Hispanic ethnicity

Psych. NOS = psychosis NOS

SCZ = schizophrenia

SCZform = schizophreniform

SCzaff = schizoaffective disorder

Smoking = smoking cigarettes at study entry

Alcohol, Marijuana and Other drugs = use of these substances at study entry

Table 1

Characteristics of 404 RAISE-ETP Subjects

	Mean	**95% CI**	**Median**
Age	23.6 years	(23.1, 24.1)	22 years
		Number	Percent of subjects
Male Sex		N=293	72.5%
Racial background			
	Caucasian	N=218	54%
	African-American	N=151	37.4%
	American Indian	N=22	5.4%
	Asian	N=12	3%
	Pacific Islander	N=1	0.2%
Hispanic ethnicity		N=73	18.1%
Had a psychiatric hospitalization prior to enrollment		N=316	78.2%
Diagnosis at study entry			
	schizophrenia	N=214	53%
	schizophreniform disorder (provisional)	N=57	14.1%
	schizophreniform disorder (definite)	N=10	2.5%
	schizoaffective disorder, bipolar type	N=24	5.9%
	schizoaffective disorder, depressive type	N=57	14.1%
	brief psychotic disorder	N=2	0.5%
	psychotic disorder NOS	N=40	9.9%
Currently using substances at study entry			
	Cigarettes[1]	N=207	51.4%
	Alcohol	N=113	28.0%
	Marijuana	N=96	23.8%
	other drugs of abuse[1]	N=10	2.5%
Geographic location where receiving treatment			
	North	N=69	17.1%
	South	N=89	22.0%
	Mid-West	N=154	38.1%
	West	N=92	22.8%
Insurance[2]			
	private or private and public	N=82	20.4%
	public only	N=127	31.7%
	no insurance	N=173	43.1%
	Insurance status not known by subject	N=19	4.7%

[1] status not assessed for 1 subject

[2] status not assessed for 3 subjects

Table 2

Frequency Of Prescription Of Major Medication Classes[1]

Medication class	Number of subjects prescribed a class	Percent of all subjects
No medication	48	11.9%
Only medications for general medical conditions	3	0.7%
Antipsychotics	337	83.4%
Antidepressants	129	31.9%
Mood stabilizer	37	9.2%
Anti-anxiety agent	42	10.4%
Sedative hypnotic	20	5.0%
Opiate analgesics	7	1.7%
Opioid replacement addiction medications	2	0.5%
Stimulants	5	1.2%
Non-stimulant ADHD medication	1	0.2%
α_2 adrenergic agonist	3	0.7%

[1] subjects could be prescribed more than 1 agent in a class

Table 3

Prescriptions For A Single Antipsychotic 300 Subjects

Medication	Number of subjects prescribed a medication (may be prescribed several formulations)[1]	Percent	Number prescribed oral formulation only or long acting formulation only	Median dose (mg) [2]	Mean dose (mg) [2]	95% CI	Dose range (mg) [2]	Number prescribed higher than 2009 PORT dosing for multi-episode patients	Number prescribed higher than 2009 PORT dosing for first episode patients[3]
risperidone	109	36.3%							
			Oral =107	3 [5]	2.9 [5]	2.6, 3.2	0.25–7.0 [5]	0 [5]	8[5]
			Long Acting =1	75	--		--	N/A	N/A
olanzapine	51	17.0%	Oral = 51	15 [6]	16.5 [6]	14.2, 18.7	2.5–40 [6]	8 [6]	22[6]
aripiprazole	35	11.7%	Oral = 35	10 [7]	10.0 [7]	8.3, 11.7	2–20 [7]	0 [7]	N/A
paliperidone	30	10.0%							
			Oral =17	6	5.8	4.7, 7.0	3–9	0	N/A
			Long Acting = 13	136.5 [7]	149.5 [7]	121.9, 177.1	117–234 [7]	N/A	N/A
quetiapine	28	9.2%	Oral = 28	300 [7]	309.7 [7]	233.5, 386.0	20–800 [7]	1 [7]	N/A
haloperidol	21	7%							
			Oral =12	10 [7]	11.3 [7]	6.4, 16.1	3–30 [7]	3 [7,8]	N/A
			Long Acting = 4	75	81.2	21.6, 140.9	50–125	N/A	N/A
ziprasidone	12	4.0%	Oral = 12	80 [9]	102.2 [9]	57.8, 146.7	40–200 [9]	1 [9]	N/A
lurasidone	4	1.3%	Oral = 4	40 [7]	66.7 [7]	0, 181.4	40–120 [7]	N/A	N/A
asenapine	2	0.7%	Oral = 2	10	10		10	N/A	N/A
Clozapine	2	0.7%	Oral = 2	250	250	0,885.3	200–300	0	N/A
thiothixene	2	0.7%	Oral = 2	5	5		5	0	N/A
chlorpromazine	1	0.3%	Oral = 1	--[7]	--[7]		--[7]	--[7]	N/A
fluphenazine	1	0.3%	Oral = 1	15	15		15	1[8]	N/A
loxapine	1	0.3%	Oral = 1	40	40		40	0	N/A
perphenazine	1	0.3%	Oral = 1	4	4		4	0	N/A

N/A = not applicable

[1] because some subjects were prescribed an oral and a long acting formulation of the same medication, the number of subjects who are prescribed a medication may be larger than the sum of the number prescribed only oral and only long acting formulations;

[2] for subjects prescribed only oral medications or subjects prescribed only long acting medications; dose is total daily dose for oral medications and total dose per month for long acting medications (e.g. 75 mg for a subject receiving two 37.5 mg injections within a month period);

[3] upper daily dose range limit of 15 mg for olanzapine and 5 mg for risperidone based upon 2009 PORT recommendations;

[4] for subjects prescribed only long acting medication;

[5] dosing data not available for 4 subjects;

[6] dosing data not available for 2 subjects;

[7] dosing data not available for 1 subject;

[8] based on 2009 PORT maintenance therapy dose range;

[9] dosing data not available for 3 subjects;