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Psychotropic medication use in youth at high risk for psychosis: Comparison of baseline data from two research cohorts 1998–2005 and 2008–2011

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ABSTRACT

Background: Antipsychotic medication use rates have generally been rising among youth with psychiatric disorders, but little is known about use rates of antipsychotics or other psychotropic medications in patients at high risk for psychosis.
Method: Baseline psychotropic medication use rates were compared in two research cohorts of patients at high risk for psychosis that enrolled between 1998–2005 (n = 391) and 2008–2011 (n = 346). Treatment durations and antipsychotic doses were described for cohort 2.
Results: Median age was 17 years in cohort 1 and 18 years in cohort 2. The rate of prescription of any psychotropic at baseline was roughly 40% for each cohort. Antipsychotic prescription rates were 24% among sites that permitted baseline antipsychotic use in cohort 1 and 18% in the cohort 2; the decline did not quite reach statistical significance ($p = 0.064$). In cohort 2 the mean ± SD baseline chlorpromazine-equivalent dose was 121 ± 108 mg/d, and lifetime duration of antipsychotic treatment was 3.8 ± 5.9 months.
Discussion: Although the rate of antipsychotic prescription among high-risk youth may have fallen slightly, the nearly one-in-five rate in the second cohort still constitutes a significant exposure. Mitigating factors were that doses and durations of treatment were low. As for other nonpsychotic conditions, it is incumbent on our field to develop alternative treatments for high-risk patients and to generate additional evidence for or against the efficacy of antipsychotics to help define their appropriate role if alternative treatments fail.

1. Introduction

Antipsychotic prescription in adolescents increased approximately four-fold in the US between 1993–1998 and 1999–2004 and then another roughly 40% by 2005–2009 (Olfson et al., 2012). Use in adolescents in Canada has also increased (Pringsheim et al., 2011), and similar findings have been reported from Europe (Zuddas et al., 2011). The change does not primarily represent increased use for psychotic disorders; rather the increase is mostly or entirely seen in non-psychotic patients (Pringsheim et al., 2011; Olfson et al., 2012). Some antipsychotic medications do have FDA-approved uses in non-psychotic disorders (Christian et al., 2012), particularly for children and adolescents. Antipsychotic use has been rising in adult patients also (Alexander et al., 2011; Maher et al., 2011), but the increase may be of especial concern in youth since metabolic adverse effects appear even more frequent in young patients (Woods et al., 2002; Gebhardt et al., 2009; Safer, 2011; Kryzhanovskaya et al., 2012).

The risk syndrome for psychosis (Woods et al., 2009) is a non-psychotic condition under increasing investigation over the past two decades (Klosterkoetter et al., 2011; Fusar-Poli et al., 2013). Also known by other names including 'at-risk mental state' and 'ultra-high-risk', the risk syndrome is based on earlier retrospective

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observations of subsyndromal or "attenuated" positive symptoms in the months or years preceding frank onset of schizophrenia (Yung and McGorry, 1996). A recent meta-analysis of 27 studies suggested that the average prospective rate of transition to frank psychosis is 22% by one year and 36% by three years (Fusar-Poli et al., 2012a). In addition to carrying substantial risk for psychosis, risk syndrome patients meet general mental health standards for current illness (Ruhrmann et al., 2010) in that at presentation they display distressing current symptoms and functional and cognitive impairment (Woods et al., 2001, 2010b; Seidman et al., 2010; Fusar-Poli et al., 2012b; Giuliano et al., 2012). Risk syndrome patients often qualify for comorbid diagnoses of other disorders (Rosen et al., 2006; Addington et al., 2007, 2012;), and such comorbidities represent additional targets for treatment. Intervention studies have begun to address these patients' prevention and treatment needs (Stafford et al., 2013). Medication treatment studies have primarily focused on antipsychotics (McGorry et al., 2002; Woods et al., 2003, 2007; McGlashan et al., 2006; Ruhrmann et al., 2007; Yung et al., 2011) but have also included a search for alternative treatments with fewer adverse effects (Amminger et al., 2010).

Risk syndrome patients often seek and receive mental health treatment in the community (Preda et al., 2002; Cadenhead et al., 2010). The rates at which antipsychotic treatment occurs, and whether such rates are increasing, are therefore of clinical and public health interest. In the absence of epidemiologic studies, we report on community prescription of antipsychotics at baseline in two large research cohorts that recruited from 1998–2005 to 2008–2011. Prescription rates for other psychotropic medications are also included for comparison purposes.

2. Methods

The two research cohorts were ascertained by the North American Longitudinal Prodrome Study (NAPLS) group and are referred to as NAPLS-1 and NAPLS-2. Subjects under age 18 with schizotypal personality disorder (SPD) are included along with risk syndrome patients in both cohorts because evidence showed that youth with SPD were at high risk for psychosis as well, even when risk syndrome criteria were not met (Woods et al., 2009). The two groups of subjects together are referred to here as high-risk subjects.

2.1. Design, subjects, and medication methods in NAPLS-1

The NAPLS-1 study reported on 377 risk syndrome subjects at baseline (Woods et al., 2009) and 36 subjects with SPD under age 18 who did not meet risk syndrome criteria, for a total of 413 high-risk patients. Subjects enrolled between 1998 and 2005. Methods have previously been reported in detail (Addington et al., 2007). Briefly, seven mostly independent projects with broadly similar goals focused on prospectively determining outcomes of a risk syndrome diagnosis and an eighth project collecting a sample of familial high-risk subjects created a federated database. Each site utilized the Structured Interview for Psychosis-risk Syndromes (SIPS) to determine whether risk syndrome or SPD criteria were met. The SIPS adopted and adapted three sets of criteria originally articulated by the Melbourne group (Yung et al., 1996). Detailed descriptions of SIPS symptom severity scales, risk syndrome diagnostic criteria, and psychometric properties are available (Miller et al., 2002, 2003; Lencz et al., 2003, 2004; Hawkins et al., 2004; Lemos et al., 2006; Addington et al., 2007, 2012; Woods et al., 2009; McGlashan et al., 2010). Some sites in NAPLS-1 did not permit or usually did not permit subjects on antipsychotic to enroll (UNC, Toronto, Yale); the remaining sites accepted patients without regard to baseline antipsychotic use. No other psychotropic medications were exclusionary for any site. Current psychotropic medication at baseline was recorded, but no information on doses or duration. Baseline medications in the NAPLS-1 cohort have been reported previously (Walker et al., 2009; Cadenhead et al., 2010).

2.2. Design, subjects, and medication methods in NAPLS-2

The ongoing NAPLS-2 study intends to enroll 720 high-risk subjects, and the first 360 enrolled are designated as the first half sample. Subjects in the first half sample were enrolled from late 2008 to early 2011, including 344 risk syndrome subjects and 16 subjects with SPD under age 18 who did not meet risk syndrome criteria. Methods for NAPLS-2 have also been described in detail (Addington et al., 2012). All sites followed a uniform protocol for enrollment and assessment, but sites were permitted to employ ascertainment strategies that worked best locally. One site moved from Toronto to Calgary between NAPLS-1 and NAPLS-2, keeping the same principal investigator, and the Harvard site began enrolling high-risk patients with NAPLS-2; otherwise the same sites participated in both cohorts. All sites in NAPLS-2 permitted patients to enroll without regard to baseline psychotropic medication. Patient enrollment required a consensus on a SIPS risk syndrome diagnosis among conference call participants from each site. Patients and/or parents were interviewed about any psychotropic medication prescribed since birth and periods of no medication. For each medication course we collected start date, stop date, medication name, daily dose if routine, and unit dose and frequency of use if as-needed. When the patient could not remember names of medications or doses, every effort was made to obtain the information from prescribers, medical records, and pharmacies. Individual courses were then summed to obtain duration data and chlorpromazine-equivalent doses (Woods, 2003) were calculated.

2.3. Data analysis

Demographic and diagnostic measures common to the two studies that might confound medication use rates across cohorts were selected for sample comparisons (Table S1 in Supplementary Content). Analyses used SPSS, version 19. Univariate comparisons utilized chi-square for categorical measures. One-sample Kolgorov–Smirnov (K–S) tests showed that none of the continuous measure distributions were normal. For these measures samples were therefore summarized using median and range and compared using the K–S Z statistic.

Effects of demographic and diagnostic measures on medication use rates were evaluated in the combined samples using Pearson correlations, or nominal regression when characteristics were multinominal. Nominal regression models would not converge for race, and Pearson correlations with a bivariate minority vs Caucasian variable were substituted. Logistic regression was used for multivariate comparisons of current medication at baseline between NAPLS-1 and NAPLS-2 cohorts, including as covariates demographic or diagnostic measures associated with specific medication use at $p < 0.05$. When age and age <18 were both associated with medication use, the variable with the larger absolute r value was included in the model.

3. Results

3.1. Participants and medication use rates

Twenty-two patients in NAPLS-1 and fourteen in NAPLS-2 were missing baseline medication information (Table S1). The highest medication use rates (Table 1) in both cohorts were for antidepressants, followed by antipsychotics. Antipsychotic data by site (Table S2) confirmed that differences in inclusion/exclusion criteria between the two cohorts at three sites confounded a determination of change between cohort. Moreover, since antipsychotic use was correlated with antidepressant use, mood stabilizer use, and use of any and >1 psychotropic within the four sites whose inclusion/exclusion policy did not change (UCLA, Emory, Hillside, UCSD, Table S3), other medication use appeared confounded as well. Accordingly, for analyses of change in medication use rates across cohort sites were restricted to these four "qualifying sites."