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Cognitive burden of anticholinergic medications in psychotic disorders

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ABSTRACT

Background: Patients with psychotic disorders are often treated with numerous medications, many of which have anticholinergic activity. We assessed cognition in relation to the cumulative anticholinergic burden of multiple drugs included in treatment regimens of participants from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study.

Method: Clinically stable participants with schizophrenia (n = 206), schizoaffective disorder (n = 131), and psychotic bipolar disorder (n = 146) were examined. Anticholinergic properties of all scheduled drugs were quantified using the Anticholinergic Drug Scale (ADS). ADS scores were summed across individual drugs to create a total ADS burden score for each participant and examined in relation to the Brief Assessment of Cognition in Schizophrenia (BACS).

Results: Anticholinergic burden aggregated across all medications was inversely related to cognitive performance starting at ADS scores of 4 in participants with schizophrenia. Those with ADS scores ≥4 had lower composite BACS scores compared to those with ADS < 4 ($p = 0.004$). Among BACS subtests, Verbal Memory was the most adversely affected by high anticholinergic burden. Despite similar anticholinergic burden scores across groups, a significant threshold effect of anticholinergic burden was not detected in schizoaffective or psychotic bipolar disorder.

Conclusion: We identified an adverse effect threshold of anticholinergic burden on cognition in clinically stable participants with schizophrenia. This relationship was not identified in affective psychoses. Examination of other medications, doses, and clinical measures did not account for these findings. Patients with schizophrenia may have increased cognitive susceptibility to anticholinergic medications and the aggregate effects of one's medication regimen may be important to consider in clinical practice.

1. Introduction

Neuropsychological impairment is a core feature of schizophrenia (Hill et al., 2004b; Keefe et al., 2007; Lam et al., 2014). Impairments have been reported in many cognitive domains, including verbal learning and memory, verbal fluency, working memory, processing speed, and executive function (Bilder et al., 2002; Hill et al., 2004a, 2013;

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Saykin et al., 1994). Similar neuropsychological deficits, albeit less severe, are reported in other psychotic disorders (Hill et al., 2008, 2009, 2013; Lee et al., 2016). Cognitive impairment relates directly to functional outcomes in patients such as psychosocial skill acquisition, performing daily activities, and vocational attainment and contributes to poor quality of life (Green et al., 2000; Leifker et al., 2009). Identifying and minimizing factors exacerbating cognitive deficits is essential for enhancing quality of life and compliance to treatments in patients with psychotic disorders.

Medications with high anticholinergic activity may adversely affect cognition. One biological mechanism for this effect relates to the suppression of the central cholinergic system via direct blockade of muscarinic cholinergic receptors which can disrupt memory (Bartus et al., 1982; Everitt and Robbins, 1997). Among the five distinct muscarinic receptor subtypes (M1–M5), antagonism of the muscarinic M1 receptor is thought to be most closely linked to cognitive impairments, especially those involving memory processes (Everitt and Robbins, 1997). These M1 receptor relationships are linked to cognition in multiple central nervous system (CNS) disorders (Gray and Roth, 2007).

The adverse cognitive effects of anticholinergic medications are established from studies primarily in the elderly whereby anticholinergic burden is associated with increases in delirium, falls, and cognitive deficits (Ancelin et al., 2006; Campbell et al., 2009; Risacher et al., 2016). Furthermore, the aggregate contribution of numerous medications in a treatment regimen can collectively contribute to these outcomes (Campbell et al., 2016; Gray et al., 2015). Studies of anticholinergic medication effects on cognition in schizophrenia (Baitz et al., 2012; Baker et al., 1983; Brébion et al., 2004; Fayen et al., 1988; Minzenberg et al., 2004; Mori et al., 2002; Perlick et al., 1986; Strauss et al., 1990; Sweeney et al., 1991; Tune et al., 1982; Wojtalik et al., 2012) typically have smaller sample sizes and focus on specific anticholinergic medications (i.e. benztropine or trihexyphenidyl) (Baitz et al., 2012; Baker et al., 1983; Brébion et al., 2004; Fayen et al., 1988; Mori et al., 2002; Sweeney et al., 1991) used to treat movement disorder side effects of antipsychotic drugs. However, investigations considering other medications with anticholinergic properties in patient regimens are lacking and these relationships in affective psychosis are relatively understudied.

Patients with psychosis-spectrum disorders often take a number of psychotropic medications, which have varying degrees of anticholinergic properties (Chakos et al., 2006). High medical comorbidities in psychosis often result in the utilization of many non-psychotropic medications, some of which have anticholinergic properties (Carnahan et al., 2006; Jeste et al., 1996). Due to known differences in medication utilization, clinical features, and cognitive deficits across psychotic disorders (Hill et al., 2013), it is important to better understand the adverse cognitive implications of net anticholinergic burden and to examine such effects in each of these diagnoses. In the present study, we assessed cognition in relation to anticholinergic burden aggregated across all medications included in individual treatment regimens of clinically stable patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study (Tamminga et al., 2013).

2. Methods

2.1. Participants

Participants in this study were selected from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium, which is a study designed to examine an array of candidate endophenotypes including cognition across psychotic disorders (Tamminga et al., 2013). Inclusion criteria for B-SNIP included: (1) age between 15 and 65; (2) age-corrected Wide Range Achievement Test Fourth Edition (WRAT-IV) Reading Score ≥ 65; (3) sufficient English proficiency to complete cognitive testing; (4) no history of seizures or organic brain insults with loss of consciousness > 10 min; (5) no diagnosis of substance abuse in the past 30 days or substance dependence during the previous 6 months; (6) negative urine toxicology screen for commonly abused drugs the day of testing; (7) no history of unstable medical or neurological conditions (see reference (Hill et al., 2013)). We focused on a subgroup of B-SNIP probands (206 schizophrenia, 131 schizoaffective, and 146 psychotic bipolar disorder) who were taking at least one antipsychotic medication and had detailed dosing information available. Given the known relationships of dopamine antagonism properties and cognition (Reilly et al., 2006; Sweeney et al., 1991), we selected patients with antipsychotic exposure that could be consistently examined across diagnoses in our analyses.

DSM-IV diagnoses were established via consensus diagnostic meetings using information obtained from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1995), available medical charts, and interviews with relatives. Clinical symptom assessments included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Young Mania Rating Scale (YMRS) (Young et al., 1978), and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The Schizo-Bipolar Scale (SBS) ranging from 0 (the most bipolar-like disorder) to 9 (the most schizophrenia-like disorder) (Keshavan et al., 2011) was also assessed in relation to medication variables. All patients were clinically stable with no major changes in medication regimen for at least 4 weeks. Institutional review board approvals were obtained at each B-SNIP site (Hartford, Baltimore, Chicago, Dallas, Boston and Detroit). After the study was explained in detail, all participants provided written informed consent.

2.2. Medication assessments

A medication history interview was performed for both prescription and non-prescription medications. Estimated anticholinergic potency was assigned a numerical value for each scheduled medication in regimens using an updated version of the Anticholinergic Drug Scale (ADS) (Carnahan et al., 2006). This is currently the most comprehensive scale available to quantify anticholinergic burden for the majority of medications commonly used to treat psychotic symptoms and has been validated against serum anticholinergic activity (SAA) (Carnahan et al., 2006). Since the initial development of the ADS, additional information about the anticholinergic properties of some older medications (Chew et al., 2008; http://kidbdev.med.unc.edu/databases/kidb.php; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/), as well as newly available medications with anticholinergic properties, were incorporated for the current analyses. Examples include modification of scores for selected medications (i.e. olanzapine, quetiapine, etc.) based on more recent reports of anticholinergic activity (Chew et al., 2008) and available inhibitory constant (Ki) values for muscarinic receptors (http://kidbdev.med.unc.edu/databases/kidb.php; http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). The original ADS is available in Carnahan et al. (2006), and the updated items for this analysis are highlighted in Supplement Table 1. Supplement Table 2 shows the number of participants for each total ADS score. Total ADS scores for each patient were calculated by summing the values of all scheduled medications used by each participant. Total ADS scores based on the aggregate accumulation of many medications each with different anticholinergic burden values were not normally distributed (due to many participants having no exposure), and the linear nature of ADS scores in relation to serum anticholinergic activity has not been established. Thus ADS scores were treated as ordinal data (0, 1, 2, 3, 4, 5…12).

Finally, to estimate relative antipsychotic dose, a chlorpromazine dose equivalent (CPZeq) was calculated using the Andreasen method (Andreasen et al., 2010). CPZeq was not normally distributed and required a log transformation to normalize the distribution in each diagnostic group for statistical analyses.

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