Neuroscience and Biobehavioral Reviews 37 (2013) 1162–1171

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

# Systematic review: Pharmacological treatment of tic disorders – Efficacy of antipsychotic and alpha-2 adrenergic agonist agents

Hannah Weisman[a], Imraan A. Qureshi[b], James F. Leckman[a], Lawrence Scahill[b,c], Michael H. Bloch[a,b,*]

[a] Yale Child Study Center, Yale University School of Medicine, New Haven, CT, United States
[b] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States
[c] School of Nursing, Yale University School of Medicine, New Haven, CT, United States

ARTICLE INFO

*Article history:*
Received 17 July 2012
Received in revised form 5 September 2012
Accepted 17 September 2012

*Keywords:*
Antipsychotic agents
Alpha-2 adrenergic agonist
Tic disorders
Attention-deficit/hyperactivity disorder
Meta-analysis

ABSTRACT

We conducted a meta-analysis of randomized, placebo-controlled trials to determine the efficacy of antipsychotic and alpha-2 agonists in the treatment of chronic tic disorders and examine moderators of treatment effect. Meta-analysis demonstrated a significant benefit of antipsychotics compared to placebo (standardized mean difference (SMD) = 0.58 (95% confidence interval (CI): 0.36–0.80). Stratified subgroup analysis found no significant difference in the efficacy of the 4 antipsychotic agents tested (risperidone, pimozide, haloperidol and ziprasidone). Meta-analysis also demonstrated a benefit of alpha-2 agonists compared to placebo (SMD = 0.31 (95% confidence interval CI: 0.15–0.48). Stratified subgroup analysis and meta-regression demonstrated a significant moderating effect of co-occurring ADHD. Trials which enrolled subjects with tics and ADHD demonstrated a medium-to-large effect (SMD = 0.68 (95%CI: 0.36–1.01) whereas trials that excluded subjects with ADHD demonstrated a small, non-significant benefit (SMD = 0.15 (95%CI: −0.06 to 0.36). Our findings demonstrated significant benefit of both antipsychotics and alpha-2 agonists in treating tics but suggest alpha-2 agonists may have minimal benefit in tic patients without ADHD.

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**Contents**



* Corresponding author at: Child Study Center, Yale University School of Medicine, PO Box 2070900, New Haven, CT 06520, United States. Tel.: +1 203 974 7551; fax: +1 203 785 7611.
*E-mail address:* michael.bloch@yale.edu (M.H. Bloch).

0149-7634/$ – see front matter. Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.neubiorev.2012.09.008

## 1. Introduction

Tourette syndrome (TS) is a neurodevelopmental tic disorder characterized by the presence of both motor and vocal (phonic) tics for at least a year in duration (DSM, 2000). Tic symptoms typically have an onset around the age 5 or 6 years and reach their worst-ever severity around 10–12 years of age (Leckman et al., 1998). Approximately one half to two thirds of adolescents with TS will have a decrease in tic severity by early adulthood (Leckman et al., 1998; Bloch et al., 2006). For the rest of these adolescents, the persistence of tics into adult life may have detrimental effects on quality of life. Some tics may be self-injurious, while others, such as coprolalia, may be disruptive in the social environment (Erenberg et al., 1987).

Antipsychotics are generally recognized by experts as the most effective pharmacological treatment for tics (Waldon et al., 2012; Singer, 2010; Scahill et al., 2006; Roessner et al., 2012). Two antipsychotic medications, haloperidol and pimozide, are the only two FDA approved treatments for tics, although they are not currently recommended as the first-line pharmacotherapy because of their adverse side-effect profile. Possible side effects of antipsychotics include weight gain, sedation and cognitive blunting, parkinsonism, dyskinesia, and akathisia (Scahill et al., 2006).

Although generally recognized as not as effective as antipsychotic medications, alpha-2 agonists including clonidine and guanfacine are often used as the first-line pharmacological treatment for tics because of their more benign safety profile (Singer, 2010; Scahill et al., 2006; Bloch, 2008; Swain et al., 2007; Roessner et al., 2011). As written by the Tourette Syndrome Medical Advisory Board, "For tics of moderate or greater severity, guanfacine or clonidine may be considered as the first line given the favorable safety margin of these medications." (Scahill et al., 2006) Guanfacine although widely utilized for the treatment of tics in the United States, is not available in many European countries. Alpha-2 agonists also have the advantage of being effective in the treatment of ADHD in patients with and without tics (Bloch et al., 2009; Connor et al., 1999). In clinically ascertained samples, more than half of children with TS also have ADHD (Khalifa and von Knorring, 2006). Historically, using clonidine as the prototype, the alpha-2 agonists were presumed to exert therapeutic befits by turning down arousal resulting in more optimal regulation of norepinephrine subcortical and cortical circuits (Arnsten, 2010). Accumulated evidence from animal studies suggest that the alpha-2 agonists enhance the functional connectivity of prefrontal cortical networks through stimulation of post-synaptic alpha-2A receptors on the dendritic spines of prefrontal cortical pyramidal cells (Arnsten, 2010; Wang et al., 2007). This mechanism, which may apply more specifically to guanfacine than clonidine, implies that alpha-2 agonists may increase the effectiveness of the frontal cortex in regulating attention and suppressing tics (Arnsten, 2010). Although alpha-2 agonists are commonly used as first-line treatment for children with tics, research to date has not rigorously examined the efficacy of these medications in treating tics in children with and without ADHD.

Several influential professional organizations, the American Academy of Child and Adolescent Psychiatry (AACAP), the Canadian Academy of Child and Adolescent Psychiatry (CACAP) and the European Society for the Study of Tourette Syndrome (ESSTS) have recently or are currently developing guidelines in the pharmacological treatment of TS (Roessner et al., 2011; Pringsheim et al., 2012). These treatment guidelines have or are currently considering making treatment recommendations between and within these classes of pharmacological agents. Therefore quantitative meta-analysis summarizing the current evidence of efficacy of different antitic medications is timely. Previous systematic reviews in the area have been narrow in scope (confined to atypical or typical antipsychotics separately), and have not performed quantitative synthesis of data from available trials (Pringsheim et al., 2012; Pringsheim and Marras, 2009).

The purpose of this meta-analysis is to compare existing randomized, controlled trials of alpha-2 agonists and antipsychotics to determine their efficacy in treating tic disorders. In meta-analysis of trials involving antipsychotic agents, our goal was to determine the average effect size (compared to placebo) of antipsychotics as a class and determine if there was any evidence that individual antipsychotic agents differ in efficacy. We also conducted stratified subgroup analysis and meta-regression to determine if dose and duration of antipsychotic treatment or trial methodological quality influenced the estimated efficacy of antipsychotics. In meta-analysis of trials involving alpha-2 agonists, we sought to determine the average effect size (compared to placebo) of alpha-2 agonists as a class and examine moderators of treatment effect. We hypothesized that alpha-2 agonists would be significantly more efficacious in treating tics of patients accompanied by ADHD compared to those without ADHD.

## 2. Methods

### 2.1. Search strategy

Two reviewers (HW and MHB) searched PubMED (1965–October 2011) (for relevant trials using the search strategy ("Antipsychotic Agents" [Pharmacological Action] OR "Antipsychotic Agents" [Mesh]) AND tic disorders) to locate trials of antipsychotic agents and ("Adrenergic alpha-2 Receptor agonists [Pharmacological Action]" AND "Tic Disorders" [Mesh]) to locate trials of alpha-2 agonist medications. The results of the search were further limited to randomized control trials. The references of eligible trials as well as any appropriate review articles in this area were additionally searched for citations of further relevant published and unpublished research. There were no language limitations on our search strategy.

### 2.2. Criteria for inclusion of studies in this review

Studies were included in this meta-analysis if they were randomized, controlled trials examining the efficacy of FDA-approved antipsychotic agent medications or alpha-2 adrenergic agonists