Time to Response to Citalopram Treatment for Agitation in Alzheimer Disease

Daniel Weintraub, M.D., Lea T. Drye, Ph.D., Anton P. Porsteinsson, M.D., Paul B. Rosenberg, M.D., Bruce G. Pollock, M.D., Ph.D., Devangere P. Devanand, M.D., Constantine Frangakis, Ph.D., Zahinoor Ismail, M.D., Christopher Marano, M.D., Curtis L. Meinert, Ph.D., Jacobo E. Mintzer, M.D., M.B.A., Cynthia A. Munro, Ph.D., Gregory Pelton, M.D., Peter V. Rabins, M.D., Lon S. Schneider, M.D., David M. Shade, J.D., Jerome Yesavage, M.D., Constantine G. Lyketsos, M.D., M.H.S., for the CitAD Research Group

Objective: *Agitation is a common and significant problem in Alzheimer disease (AD). In the recent Citalopram for Agitation in Alzheimer's Disease (CitAD) study, citalopram was efficacious for the treatment of AD agitation. Here we examined the time course and predictors of response to treatment.* **Methods:** *Response in CitAD was defined as a modified Alzheimer Disease Cooperative Study Clinical Global Impression of Change (CGIC) score of 1 or 2 or a Neurobehavioral Rating Scale agitation subscale (NBRS-A) score reduction $\geq$ 50% from baseline. "Stable early response" was defined as meeting the aforementioned criteria at both weeks 3 and 9, "late response" was response at week 9 but not at week 3, and "unstable response" was response at week 3 but not at week 9.* **Results:** *In the primary analyses, citalopram was superior to placebo on both the CGIC and the NBRS-A response measures. Little between-group differences were found in response rates in the first 3 weeks of the study (21% versus 19% on the CGIC). Citalopram patients were more likely than placebo patients to be a late responder (18% versus 8% on CGIC, Fisher's exact $p = 0.09$; 31% versus 15% on NBRS-A, Fisher's exact $p = 0.02$). Approximately half of citalopram responders (45%–56%) at end of study achieved response later in the study compared with 30%–44% of placebo responders.* **Conclusion:** *Treatment with citalopram for agitation in AD needs to be at least 9 weeks in duration to allow sufficient time for full response. Study duration is an important factor to consider in the design of clinical trials for agitation in AD.* (Am J Geriatr Psychiatry 2015; ■:■–■)

Key Words: Agitation, Alzheimer disease, citalopram

Received November 18, 2014; revised May 7, 2015; accepted May 12, 2015. From the Perelman School of Medicine (DW), University of Pennsylvania, Philadelphia, PA; Johns Hopkins Bloomberg School of Public Health (LTD, CF, CLM, DMS), Baltimore, MD; University of Rochester School of Medicine and Dentistry (APP), Rochester, NY; Johns Hopkins Bayview and Johns Hopkins School of Medicine (PBR, CM, CAM, PVR, CGL), Baltimore, MD; Campbell Institute (BGP), Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada; Division of Geriatric Psychiatry (DPD, GP), New York State Psychiatric Institute and College of Physicians and Surgeons of Columbia University, New York, NY; Departments of Psychiatry and Neurology (ZI), Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada; Clinical Biotechnology Research Institute (JEM), Roper St. Francis Healthcare, Charleston, SC; University of Southern California Keck School of Medicine (LSS), Los Angeles, CA; and Stanford University School of Medicine and VA Palo Alto Health Care System (JY), Stanford, CA. Send correspondence and reprint request to Daniel Weintraub, M.D., Perelman School of Medicine at the University of Pennsylvania, 3615 Chestnut St., #330, Philadelphia, PA 19104. e-mail: daniel.weintraub@uphs.upenn.edu

http://dx.doi.org/10.1016/j.jagp.2015.05.006

INTRODUCTION

Agitation is common, persistent, and associated with adverse consequences for patients with Alzheimer disease (AD). To date, pharmacologic treatments have not been consistently effective,[1] and there is a known mortality risk from antipsychotic treatment.[2] The primary objectives of the Citalopram for Agitation in Alzheimer's Disease Study (CitAD) were to evaluate the efficacy and safety of citalopram for agitation in patients with AD.[3,4]

In brief, CitAD was a multicenter, randomized, placebo-controlled, double-blind, parallel group trial of patients with probable AD and clinically significant agitation conducted at eight academic centers in the United States and Canada.[4] Participants were randomized to receive a psychosocial intervention plus either citalopram (N = 94) or placebo (N = 92) for 9 weeks. Dosing began at 10 mg/day with planned titration to 30 mg/day over 3 weeks, with lower doses allowed if tolerability was an issue. The primary outcome measures were the Neurobehavioral Rating Scale, agitation subscale (NBRS-A) and the modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (CGIC). The study enrolled 186 participants (citalopram: 94, placebo: 92). Mean age was 78 years, 46% were women, 65% were white and non-Hispanic, 89% were community dwelling, and the mean duration of AD was 5 years. About two-thirds took cholinesterase inhibitors and just over 40% memantine. Over 90% of both groups completed the 9-week trial, and about 80% remained on treatment. At week 9, 78% of the sample was receiving 30 mg citalopram daily and 15% were receiving 20 mg citalopram daily. In terms of outcomes, citalopram was superior to placebo on both primary outcome measures but was associated with an increased QTc interval on electrocardiogram and higher rates of fever and mild gastrointestinal adverse events.

In clinical practice clinicians need to know the general time course of response to a symptomatic therapy. For example, guidelines for antidepressant therapy recommend that if response is absent or minimal after 3–4 weeks of treatment, consideration should be given to increasing the dose or switching to another antidepressant, whereas if the depression shows partial improvement by 4 weeks, treatment should be continued for another 2–4 weeks.[5] For late-life depression, a lack of at least partial response by week 4 of an antidepressant course suggests a high likelihood of lack of remission at week 12.[6]

Correspondingly, important treatment decisions apply when managing AD patients with agitation, but there is limited evidence to guide clinical practice.[7] Given recommendations to use behavioral interventions[8] and to study other psychotropic medications (e.g., antidepressants,[9] cholinesterase inhibitors[10]) for agitation in AD, guidance for use in clinical care is needed. Because agitation is disruptive for both patient and care provider, there is an urgency to produce symptomatic improvement. Thus, clinicians need to balance symptom severity and tolerability from the start of treatment, with an eye toward making adjustments in a timely fashion. However, the pressure to do this must be tempered by evidence about time course of response to a given treatment to avoid premature medication discontinuation or dose escalation.

Using CitAD data, we performed exploratory analyses to examine the time course of treatment response across the 9 study weeks, characterizing patients as stable early responders, unstable responders, or late responders. We also examined clinical predictors of late versus early response.

METHODS

Study Design and Outcome Measures

The methods for CitAD have been published.[3] The primary definitions of response were 1) a CGIC score of 1 or 2 ("marked improvement" or "moderate improvement") or 2) an NBRS-A score reduction $\geq$ 50% from baseline to end-of-study, considered separately. Response definitions that incorporated the two outcome measures together were also applied, one more stringent (i.e., responder on *both* CGIC and NBRS-A) and the other less stringent (i.e., responder on *either* CGIC or NBRS-A, considered together). For the purposes of these analyses, "stable early response" was defined as meeting the aforementioned criteria for response at both weeks 3 and 9. "Late response" was defined as meeting criteria for response at week 9 but not at week 3. Finally,