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Platinum Priority – Incontinence

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Randomised, Multicentre, Placebo-controlled, Double-blind Crossover Study Investigating the Effect of Solifenacin and Oxybutynin in Elderly People with Mild Cognitive Impairment: The SENIOR Study

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Abstract

Background: Compared with younger people, the elderly are more likely to suffer from overactive bladder (OAB) and to have other chronic conditions that affect physical or cognitive function. Despite this, there are few data on the cognitive safety of antimuscarinic agents in older patients and none that examine the effect of these agents on those with mild cognitive impairment (MCI).
Objective: To evaluate cognitive effects during chronic stable dosing with solifenacin and oxybutynin versus placebo in older (≥75 yr) subjects with MCI.
Design, setting, and participants: A randomised, double-blind, triple-crossover trial in 26 elderly volunteers with MCI. Cognitive function was assessed using Cognitive Drug Research (CDR) computerised testing.
Intervention: Three treatment periods of 21 d each with solifenacin 5 mg once daily, oxybutynin 5 mg twice daily, or placebo, separated by 21-d washout periods.
Outcome measurements and statistical analysis: The primary end point was change from baseline in cognitive function with solifenacin at 6 h postdose and oxybutynin at 2 h postdose (time points close to their predicted time to peak concentration). Secondary end points included change in cognitive function at additional time points, and safety and tolerability assessments.
Results and limitations: Neither agent was associated with significant changes from baseline in any of the five standard, composite outcomes of cognitive function (power of attention, continuity of attention, quality of working memory, quality of episodic memory, and speed of memory). In a secondary analysis, oxybutynin was associated with significant decreases in power and continuity of attention versus placebo at 1–2 h postdose. Both agents were well tolerated, with the most frequently reported adverse event being mild or moderate dry mouth.
Conclusions: Solifenacin had no detectable effect on cognition in this group of elderly people with MCI.

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1. Introduction

Overactive bladder (OAB) is characterised by urinary urgency with or without urge incontinence, usually accompanied by urinary frequency and nocturia [1], and is estimated to affect 12–22% of the overall population [2]. Its prevalence increases with age, affecting up to 49% of men and 51% of women aged ≥75 yr [3]. Older people are more likely to take multiple medications, many of which increase the risk of incontinence, and to have chronic conditions that affect cognitive or physical function, making compensation for urinary urgency more difficult [4].

Antimuscarinic drugs are the first-line pharmacological treatment for OAB, reducing micturition frequency, urgency episodes, and urgency incontinence, and lessening the severity of symptoms [5]. However, these agents also act on central nervous system (CNS) muscarinic receptors, which have an important role in cognition [6]. Oxybutynin, commonly used to treat OAB, has a high propensity to cross the blood–brain barrier [6], and has been associated with cognitive impairment in the elderly, most likely as a result of central anticholinergic activity mediated mainly via M1 and M2 receptors in the CNS [7]. Older people may be more vulnerable to the effects of antimuscarinic agents because of age-related reductions in cholinergic receptors and altered drug metabolism and elimination. Furthermore, the permeability of the blood–brain barrier increases with age [6], Alzheimer's disease [8], diabetes [9], and multiple sclerosis [10], increasing the potential for CNS effects of antimuscarinic agents. Many clinicians are therefore wary of prescribing antimuscarinics to elderly patients, despite their documented efficacy [11].

The cognitive effects of OAB medications have been examined in cognitively intact patients [12–15], but little is known about the cognitive safety of these agents in older people with cognitive impairment, who may be more at risk. Better understanding of these potential effects is needed in such patients. This study compared the cognitive effects of treatment with 5 mg solifenacin (once daily), 10 mg oxybutynin (5 mg twice daily), or placebo in elderly volunteers with mild cognitive impairment (MCI).

2. Patients and methods

2.1. Study design

This was a randomised, double-blind, triple-crossover trial conducted at three UK commercial trial centres with experience in MCI studies. Three treatment periods of 21 d were each separated by 21-d washout periods (Fig. 1). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, and International Conference on Harmonisation guidelines, and applicable laws and regulations. The protocol was reviewed by the Brent Medical Ethics Committee, Harrow, Middlesex, UK. All subjects provided written informed consent. The trial is registered with ClinicalTrials.gov (identifier: NCT01126424).

2.2. Participants

The study enrolled men and women aged ≥75 yr with MCI as assessed by the investigator applying Stockholm criteria [16]. Because of ethical concerns regarding the potential effect of antimuscarinics in those with preexisting cognitive impairment, subjects with a Mini-Mental State Examination (MMSE) score ≤23 were excluded [17]. Subjects were required to have a body mass index of 18.0–30.0 kg/m^2. Exclusion criteria included a short-form Geriatric Depression Scale (GDS) [18] score ≥5, and a history or risk of urinary retention or current medication to treat OAB. Subjects were requested not to take stimulants such as caffeine or tobacco within 1 h prior to the cognitive function tests. All other concomitant medication, at stable dosing, was allowed.

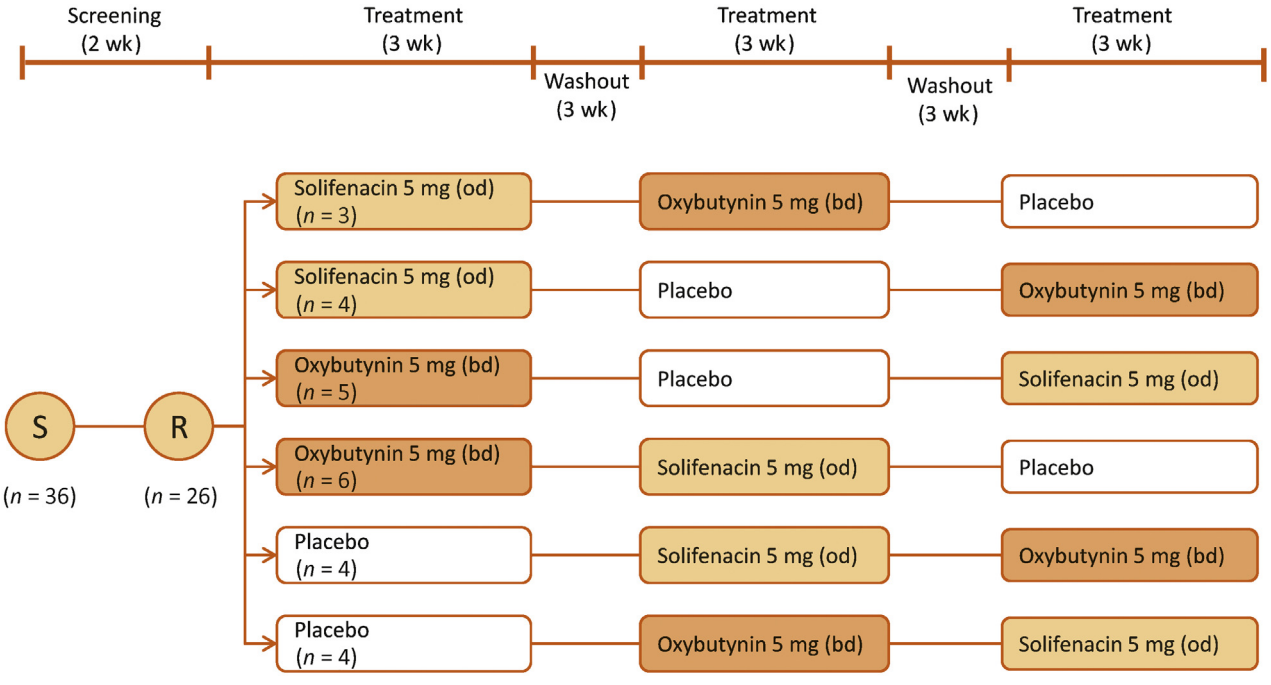

Fig. 1 – Study design. bd = twice daily; od = once daily; S = subjects; R = randomised subjects.