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Could Reduced Fluid Intake Cause the Placebo Effect Seen in Overactive Bladder Clinical Trials? Analysis of a Large Solifenacin Integrated Database

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Abstract

OBJECTIVE

To assess the hypothesis that patients receiving placebo in overactive bladder (OAB) trials who experience less benefit from 'treatment' continue with behavioral modifications such as fluid restriction, whereas those on active treatment adopt more normal drinking patterns. This may manifest itself as a reduction in micturition frequency (MF).

MATERIALS AND METHODS

We interrogated a large integrated database containing pooled patient data from 4 randomized, placebo-controlled phase III OAB solifenacin studies. A statistical correction was applied to MF to remove the influence of fluid intake.

RESULTS

Pooled analysis using patient-level data from 3011 patients and accounting for the studies within the models showed that all patients voided progressively less total urine per 24 h during treatment than at baseline. However, reduction in total urine volume voided per 24 h was larger in patients receiving placebo versus those on solifenacin; with a substantial decrease in 24 h urine output in the placebo group from baseline to Week 4, which was not the case in active groups. After correcting MF for volume voided for each patient using the statistical correction and averaging the corrected MF per treatment arm, the placebo effect almost disappeared. Patients

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on solifenacin voided less often, with a statistically significant increase in volume voided each time they voided, versus placebo.

CONCLUSIONS

Assuming volume voided is a good surrogate measure for fluid intake, this analysis shows that fluid restriction almost completely explains the reduction in MF in the placebo group. In contrast, patients receiving active treatment adopt more normal drinking patterns once they start to perceive improvement in their OAB symptoms.

INTRODUCTION

Placebo response is a well-recognized phenomenon in clinical trials, and is generally higher with chronic disorders, in which patients experience bother or pain, than in disorders involving objectively measured parameters[1]. A substantial placebo effect is generally observed in overactive bladder (OAB) trials[1-3], making it occasionally difficult to quantify the benefit of active treatments[4,5].

Several hypotheses have been suggested for this substantial placebo effect. Receiving a placebo is not the same as 'no treatment', but is part of a package of care in which a patient receives general advice, has his or her urine tested for infection and has any infection treated, sees the doctor or nurse who is carrying out the study, fills in a bladder (micturition) diary on a regular basis, and in some countries is given free medication, for which he or she would otherwise have to pay. Therefore, the placebo response seen in these trials could be due to all non-drug aspects of the trial, in addition to 'treatment' with placebo[6]. Participating in an OAB clinical trial, which involves completing bladder diaries, usually for the first time, and interacting with healthcare professionals inevitably results in a bladder training effect. Patients also gain a greater degree of knowledge and insight into their condition from reading the patient information leaflets. The bladder diary gives the patient visual feedback of 'performance', hence they may also 'hold on' to improve the outcome of

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the bladder diary, leading to better reported responses. Patients may also learn to empty their bladders pre-emptively before a critical volume is reached by adopting a 'just in case' approach to going to the toilet. Another contributory factor is that patients may seek help when their symptoms are at their worst, and there may be a contribution from symptoms tending to naturally return towards the individual's baseline norm (regression towards the mean)[6].

A part of bladder training is to actively encourage patients to drink less as part of the educational program. The International Consultation on Incontinence (ICI) guidelines recommend behavioral modifications, including fluid manipulation, as part of first-line treatment for OAB. The average fluid intake required for normal bodily functions is about 24 mL/kg of body weight/day in a temperate climate[7]; equating to 1.68 L/day for a 70 kg person. Logically, an increase in daily fluid intake is related to an increase in the volume of urine voided daily[8]. Conversely, decreasing fluid intake can improve urinary symptoms in patients with OAB[7,9,10]. A randomized, prospective crossover trial in adults with OAB symptoms showed that a reduction of 25% in fluid intake from baseline (median 1854 ml) was effective in reducing OAB symptoms (daytime urinary frequency, urgency and nocturia)[11].

It was hypothesized that patients in a placebo group, who experience less benefit from their 'treatment', continue with behavioral modifications (such as fluid restriction), whereas those in the active group, who benefit from treatment, adopt a more normal drinking pattern. Therefore, fluid restriction itself in the placebo group may contribute to the placebo response, which is demonstrated as a reduction in micturition frequency (MF). We also postulated that there would be a difference in voided volumes between the placebo and treatment groups as a result of the fluid restriction. To assess the evidence supporting our hypothesis, we interrogated a large integrated database containing pooled patient data from 4 randomized, placebo-controlled, fixed-dose, solifenacin monotherapy studies.

MATERIALS AND METHODS

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All 4 studies were 12-week, placebo-controlled, double-blind, fixed-dose monotherapy Phase IIIa studies (**Supplementary Table 1**)[12-15]. A manuscript describing methodology for the large integrated database has been published[16].

Study endpoints based on MF can be affected directly by study medication, but may also be altered by changes in fluid intake over the course of the study. For example, if an individual has 10 micturitions per 24 h with a fluid intake of 2 L, then one would expect him/her to have 5 micturitions per 24 h with a fluid intake of 1 L. If the same individual has 7 micturitions per 24 h with a fluid intake of 1 L, then this can be considered worsening of OAB symptoms even if the absolute number of micturitions has decreased. Correction of MF follows the same principle, correcting in alignment with each individual's fluid intake at baseline and endpoint, using the following statistical correction:

MF_{base} = MF at baseline
MVV_{base} = mean volume voided/micturition (MVV) at baseline
$TotVV_{base}$ = total volume voided (TotVV) per 24 h at baseline

MF_{EoT} = MF at end of treatment (EoT) or final visit
MVV_{EoT} = MVV at EoT
$TotVV_{EoT}$ = TotVV per 24 h at EoT

$TotVV_{EoT}$ can be separated into two parts by regarding it as being equal to $TotVV_{base}$ plus the change from baseline to EoT in TotVV
ie, $TotVV_{EoT} = TotVV_{base} + \Delta TotVV$
where $\Delta TotVV = TotVV_{EoT} - ToTVV_{base}$.

As MVV is, by definition, equal to TotVV/MF, by rearrangement, MF=TotVV/MVV, and therefore

$$MF_{EoT} = TotVV_{EoT}/MVV_{EoT}$$
$$= [TotVV_{base} + \Delta TotVV)]/MVV_{EoT}$$
$$= TotVVbase/MVVEoT + \Delta TotVV/MVV_{EoT.}$$

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This can be viewed as a partition of MF_{EoT} into 2 parts as follows:
$\Delta TotVV/MVV_{EoT}$ is the additional number of micturitions/24 h (versus baseline) required to void the extra fluid intake.

$TotVVbase/MVV_{EoT}$ is the number of micturitions per 24 h that would be required at EoT to void the total daily volume, if this total volume remained unchanged from baseline, ie, if treatment did not affect subjects' fluid intake.

By applying this statistical correction, the size of the placebo effect in each evaluable patient in the dataset can be assessed.

Differences between treatment arms in total volume voided at the end of the study were analysed using an Analyis of Covariance with treatment arm and baseline as covariate.

RESULTS

The integrated database comprised pooled data from 3011 patients (**Table 1**). Average total urine voided over a 24-h period for the combined solifenacin 5 mg and 10 mg groups is shown in **Table 2**.Baseline values were lower for the solifenacin 5 mg group than for the other 2 groups (**Table 1**), but were relatively high overall (approximately 1700 ml). Pooled analysis of the patient data from the integrated database showed that patients taking solifenacin voided progressively less total urine per 24 h during the treatment period than at baseline (**Fig. 1**). However, the reduction in total urine volume voided per 24 h was larger in patients in the placebo arm (P <.0001), compared with those receiving active treatment; with a substantial decrease in 24 h urine output recorded for the placebo group from baseline to Week 4, which was not the case in the active groups. A reduction in MF from baseline to EoT was seen in both active and placebo groups; however, after correcting MF for each patient in relation to his/her volume voided and then averaging the corrected MF per treatment arm using the statistical correction described in the methods, this

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showed a stronger correction in the placebo arm than in the active treatment arm, such that the placebo effect almost completely disappeared (**Fig. 2**). Patients on solifenacin voided less often, with a statistically significant increase in volume voided each time they voided, compared with placebo.

DISCUSSION

A Cochrane review of anticholinergic drugs versus placebo for OAB in adults calculated that 41% of subjects allocated to placebo report symptomatic improvement in symptoms versus 56% in patients allocated to active treatment[3]. In addition, a systematic review of placebo-controlled, randomized trials in OAB showed that subjects who received placebo demonstrated statistically significant improvements from baseline in micturitions/day and incontinence episodes/day[17]. In common with other OAB trials, a large placebo effect has been observed in solifenacin studies. The solifenacin integrated database contains a large number of patients (>3000) from multiple studies conducted all over the world. Pooled analysis of this large integrated database showed that there was a greater reduction in volume voided over 24 h in the placebo arm than in the active arms. The logical assumption being that volume voided is a good surrogate measure for fluid intake, one can estimate the impact of reduced fluid intake on MF. It is clear from the results reported here that after adjusting for fluid intake using the statistical correction, the placebo effect almost completely disappears, and the difference between the placebo and active groups becomes bigger.

We therefore suggest that a significant component of the clinical benefit perceived by patients receiving placebo is largely due to behavioral modifications to restrict their fluid intake, which they continue throughout the duration of the trials. However, patients receiving active treatment are able to return to a more ‘normal’ drinking pattern once they start to perceive an improvement in their OAB symptoms; as a therapeutic consequence of solifenacin is to increase bladder capacity[18]. The return to normal fluid intake in the active treatment group will naturally numerically increase the number of micturitions per 24 h compared to when the patient was in a fluid-restricted state. This can limit differentiation between active treatment and

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placebo for number of micturitions per 24 hours and is also interpreted as a high placebo effect.

It should be noted in this database that baseline values for total volumes voided were relatively high. However, baseline values were lower in the solifenacin 5 mg group compared with the other groups. A possible explanation for the lower baseline values in the solifenacin 5 mg group may be that this dosing group is mainly used in European studies, whereas the 10 mg group is mainly used in US studies (**Table 1**). The US population, especially women, generally drink more than Europeans. For example, between 1977 and 1996, there was a dramatic increase in fluid consumption in the US (the consumption of bottled water increased 908% and the average soft drink portion increased by 48%)[19,20].

Limitations of this analysis are that the studies did not document changes in patient weight during the study, and that there was no direct measurement of fluid intake for any of the studies; currently, however, there is no consensus on how to measure total fluid intake with or without water from food[21]. In addition, we do not know if fluid intake had an effect on other OAB symptoms. Since the key symptoms of OAB are interlinked, it is possible that fluid intake may impact other symptoms of the OAB symptom complex including urgency or urgency urinary incontinence and contribute to the high placebo response seen in patients[12-15].

It is possible that patients in the active treatment arm increased their daily fluid intake as a result of experiencing dry mouth as an AE. However, a recent study examining the impact of dry mouth on fluid intake and OAB symptoms in women receiving fesoterodine for 10 weeks found that women experiencing dry mouth did not change their total fluid intake. In contrast, women without dry mouth significantly reduced their fluid intake (mean decrease of 172.1 mL)[22].

Theoretically, a micturition diary would have a bladder training effect in both placebo and active groups. To confirm these observations, future studies would need to include micturition diaries and measure fluid intake and voided volumes. Although frequency-volume charts would provide an accurate record of fluid intake and output, asking patients to accurately record fluid intake may add significant burden in already complex clinical trials.

CONCLUSIONS

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Active treatment was more effective than placebo in these trials. However, a high placebo effect is witnessed in OAB trials and therefore the purpose of this study was to explore a hypothesis to explain this placebo effect. Urinary volume voided over 24 hours is a good surrogate measure for fluid intake, assuming that environmental conditions do not fluctuate excessively leading to increased fluid loss. Therefore, fluid restriction could explain the reduction in MF in the placebo group and provides an alternative explanation for the placebo effect in OAB trials. We believe that it is therefore likely that a significant part of the clinical benefit perceived by patients receiving placebo is derived from behavioral modifications to restrict fluid intake, which continues throughout the duration of the trials. In contrast, patients receiving active treatment are, as a consequence of the therapeutic benefit derived from the drug, able to adopt more normal drinking patterns once they start to perceive improvement in their OAB symptoms. This return to normal fluid intake will naturally increase the number of micturitions per day compared to when the patient was in a fluid-restricted state.This can limit differentiation between active treatment and placebo for number of micturitions per day and is interpreted as a high placebo effect.

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Figure 1. Mean change from baseline to weeks 4, 8 and 12 in total urine volume voided per 24-hour period. [Single column image]

Figure 2. Change from baseline to end of study in micturition frequency/24 h. [Single column image]

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351 **Table 1.** Baseline demographics and OAB characteristics (FAS)

	Solifenacin 5 mg (N = 552)	Solifenacin 10 mg (N = 1158)	Placebo (N = 1137)
Men, N (%)	121 (21.9)	242 (20.9)	219 (19.3)
Women, N (%)	431 (78.1)	916 (79.1)	918 (80.7)
Age, mean (SD) years	56.8 (13.6)	57.9 (13.5)	58.1 (13.2)
Age range, years	19–85	18–86	18–88
Age group, years (%)			
18 to <40	55 (10.0)	115 (9.9)	99 (8.7)
40 to <65	315 (57.1)	640 (55.3)	640 (56.3)
65 to <75	130 (23.6)	277 (23.9)	277 (24.4)
≥75	52 (9.4)	126 (10.9)	121 (10.6)
BMI, mean (SD)	27.2 (5.0)	28.5 (6.3)	28.5 (6.4)
Region, N (%)			
US/Canada	0	604 (52.2)	604 (53.1)
Europe	429 (77.7)	429 (37.0)	409 (36.0)
Other	123 (22.3)	125 (10.8)	124 (10.9)

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Table 2. Average total urine volume voided over 24 h period (mL)

	Combined solifenacin 5 mg and 10 mg groups			Placebo		
	Average total urine volume voided, mL	**N**	**SD**	**Average total urine volume voided, mL**	**N**	**SD**
Baseline	1772.29	1709	711.16	1829.25	1134	775.47
Week 4	1762.61	1703	719.22	1729.27	1134	752.24
Week 8	1725.32	1614	704.44	1703.61	1066	776.79
Week 12	1695.11	1557	677.28	1679.88	1021	745.17

Difference between active treatment and placebo = 81 (95% CI = 36-125), *P* = 0.0004

Supplementary Table 1. Individual solifenacin studies included in the meta-analysis

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