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BRIEF REPORT

Depressive Symptoms and the Effectiveness of a Urate-Lowering Therapy in a Clinical Trial

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Objective. This ancillary study examined the impact of depressive symptoms on the effectiveness of a urate-lowering therapy in the context of a clinical trial.

Methods. Participants included 67 adults (ages 18–40) with elevated blood pressure who were enrolled in a double-blind, randomized, crossover clinical trial evaluating the effectiveness of allopurinol (300 mg/d) versus placebo to decrease blood pressure. Depressive symptoms were measured at the beginning of each 4-week phase with the Center for Epidemiological Studies Depression scale (CESD-10). Serum urate (sUA) was assessed at the beginning and end of each treatment phase. Compliance to treatment was measured by having detectable oxypurinol levels. Linear regressions tested associations between depressive symptoms and change in sUA in each phase, adjusting for sex and race. Logistic regression predicted compliance from depressive symptoms.

Results. Participants had a mean age of 27 years and were 64% male and 39% African American. sUA levels decreased during the allopurinol treatment period but did not change during the placebo period. Higher depressive symptoms at pretreatment were associated with an attenuated urate-lowering response during the allopurinol phase ($\beta = 0.24$, $p < 0.05$), but had no effect on sUA changes during the placebo phase. Depressive symptoms were not associated with treatment compliance assessed by oxypurinol levels.

Conclusion. Depressive symptoms were associated with reduced efficacy of allopurinol treatment for hyperuricemia in a clinical trial targeting hypertension. Studies evaluating the efficacy of urate-lowering therapies may benefit from screening for depressive symptoms.

INTRODUCTION

Hyperuricemia, typically defined as serum urate (sUA) concentration above 6.8 mg/dL (1), affects 21% of the general US population (2) and between 13% and 25% in other countries (3–6). Hyperuricemia is both central to the pathogenesis of gout (7) and has been associated with an increased risk of hypertension, cardiovascular disease, and chronic kidney disease (8–10). Urate-lowering therapies (ULTs), such as allopurinol and febuxostat, are effective at treating hyperuricemia and gout (11,12) and could have an effect on gout comorbidities (13). However, less is known about factors that may influence the effectiveness of ULTs.

ULT adherence is essential to reducing sUA levels (14), yet adherence tends to be low, especially among younger patients with gout (15). A well-established risk factor for medical nonadherence is depression, with patients who are depressed being three times more likely to be classified as nonadherent (16). The key role of depression in poor medical adherence has been observed in a variety of health conditions, including diabetes, HIV, renal disease, cancer, and asthma (16–19). Importantly, depressive symptoms affect treatment adherence even at subclinical levels (19).

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Although gout is associated with both prevalence and incidence of depression (20–23), no studies have examined the role of depressive symptoms in the effectiveness of ULTs. Additionally, little is known about the role of depressive symptoms in adherence to medications in randomized clinical trials. Thus, the main goal of this study was to evaluate the impact of depressive symptoms on the urate-lowering efficacy of allopurinol in the context of a clinical trial for adults with elevated blood pressure.

PATIENTS AND METHODS

This ancillary study reports on 67 patients who participated in the Serum Urate Reduction to Prevent Hypertension (SURPHER) study (24), a single-center, double-blinded, crossover trial in which participants were randomly assigned to 300 mg of allopurinol as ULT or to placebo (see Supplementary Figure 1 for study design). SURPHER was approved by the University of Alabama's Institutional Review Board, conducted in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines, and registered in ClinicalTrials.gov (NCT02038179). Written informed consent was obtained from all participants.

Inclusion criteria included (a) prehypertension or stage I hypertension, defined as systolic blood pressure between 120 or greater but less than 160 mm Hg or diastolic blood pressure between 80 or greater and less than 100 mm Hg; (b) sUA of 5.0 mg/dL or greater for men or 4.0 mg/dL or greater for women; and (c) age between 18 and 40 years. Each treatment period (allopurinol or placebo) was 4 weeks long; the phases were in randomized order and were separated by a 2- to 4-week washout period.

Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression Scale (CESD-10) questionnaire (25) before and after each treatment period. The 10 items inquired about symptoms of depression (eg, depressed mood, difficulty concentrating, sleep disturbances, loneliness, low energy) experienced in the last week using a four-point scale from 0 (rarely, less than 1 day) to 3 (most of the time, 5-7 days). One item ("I felt hopeful about the future") was not correlated with the other items and was removed; the remaining items were averaged and multiplied by 10 (ie, prorated) to yield scores with a possible range of 0 to 30, with higher scores indicating more depression ($\alpha = 0.76$). Scores of 8 and 10 have been considered as indicative of major depression (26). sUA was measured by the uricase reaction laboratory technique (27). Treatment compliance was assessed by measuring plasma oxypurinol levels during active treatment. A participant was considered compliant if measurable oxypurinol levels were observed at the end of the allopurinol phase.

Included and excluded participants were compared on baseline variables. Paired samples *t* test evaluated change in sUA from pre- to posttreatment during active treatment and placebo. Correlations tested bivariate associations among variables. Then, linear regressions tested associations between pretreatment depressive symptoms and change in sUA over each treatment period, adjusting for sex and race, which were associated with baseline sUA levels. The effect of pretreatment depressive symptoms on treatment compliance during the medication period was tested with logistic regression, with sex and race as covariates. A χ^2 test compared compliance between participants who received allopurinol on the first versus second phase.

RESULTS

Out of the 99 patients enrolled in the SURPHER study, 67 had complete data on depressive symptoms at the beginning of each treatment period and sUA levels before and after each treatment period. The 67 patients had a mean age 27 years (SD = 6.52, range 18-40), 39% were African-Americans, 61% were Caucasian, and 64% were males. They did not differ from those who were excluded on baseline age, sex, race, body mass index, sUA, or depressive symptoms ($p > 0.262$). Over the 4-week active treatment period with allopurinol, sUA levels decreased from a mean of 5.78 mg/dL (SD = 1.13) to 4.37 mg/dL (SD = 1.21), $p < 0.001$. However, sUA did not change during the 4-week placebo period (it was identical pre- and posttreatment means of 5.83 mg/dL, SD = 1.11 and 1.33, $p = 0.948$). Twelve of the 67 participants (18%) had baseline sUA levels above 6.8 mg/dL. Pretreatment depressive symptoms ranged from "no symptoms" (score 0) to "severe symptoms" (score 16 before allopurinol and 20 before placebo), with the mean in the "no to mild" range (mean = 4.57, SD = 4.13 before allopurinol; mean = 6.28, SD = 4.77 before placebo); 13% and 24% scored 8 or higher. In the active treatment phase, pretreatment depressive scores were associated with sUA posttreatment ($r = 0.30$, $p = 0.014$) but not pretreatment ($r = 0.14$, $p = 0.278$). During the placebo phase, pretreatment depressive scores were unrelated to sUA both pre- and posttreatment ($r = 0.06$, $p = 0.646$; and $r = 0.15$, $p = 0.240$). After adjusting for pretreatment sUA, sex, and race, pretreatment depressive scores were associated with higher levels of sUA at the end of the active treatment period ($b = 0.07$, SE = 0.03, $\beta = 0.24$, $p = 0.028$) but not at the end of the placebo period ($b = 0.03$, SE = 0.02, $\beta = 0.11$, $p = 0.102$) (see Table 1). After 4 weeks of allopurinol, the estimated difference in sUA between individuals with pretreatment depressive scores of 0 versus 16 was 1.12 mg/dL, which was similar to the average treatment effect of 1.41 mg/dL.

Based on detected oxypurinol levels at the end of the active treatment period, 43 (78%) participants were classified as compliant and 12 (22%) as noncompliant (12 had missing data). Logistic regression showed that pretreatment depressive symptoms were not associated with treatment compliance (odds ratio = 0.93, $p = 0.412$; Table 1). Compliance rates did not differ between individuals who received allopurinol in the first versus second phase ($\chi^2_{(1)} = 0.18$, $p = 0.321$).

TABLE 1. Regression models predicting posttreatment sUA or oxypurinol

	sUA postplacebo β	sUA postallopurinol β	Detected oxypurinol postallopurinol OR (95% CI)
sUA pretreatment	**0.68*** **	**0.42** **	1.38 (0.68; 2.79)
Black	0.01	0.07	0.53 (0.12; 2.28)
Male	**0.24** **	0.11	1.31 (0.25; 6.80)
Depressive symptoms	0.11	**0.24***	0.93 (0.79; 1.10)

Note. Statistically significant effects are bolded.
Abbreviations: CI, confidence interval; OR, odds ratio; sUA, serum urate.
*$p < .05$, **$p < .01$, ***$p < .001$.

DISCUSSION

To our knowledge, this is the first study evaluating the impact of depressive symptoms on the efficacy of a urate-lowering therapy within a clinical trial. The results showed that higher depressive symptoms at the beginning of the active treatment period were associated with reduced efficacy of allopurinol. In contrast to prior literature linking depressive symptoms with reduced adherence (16,18,19), this study did not find a relationship between depressive symptoms and treatment adherence. However, our study had a small sample size and might not have been adequately powered to answer the latter question.

These results contribute to our understanding of factors influencing ULT success. Although we could not provide a definitive answer about the compliance question, it is known that treatment adherence to ULT is very low, with secondary adherence (adherence past an initial phase of compliance) rates of roughly 30% (14,28). These low adherence rates have been explained by lack of information about treatment, forgetting to take medication, concerns about side effects, and increased flares in gout patients after initiating ULT (28). In the absence of a plausible biological hypothesis linking depression symptoms with lack of efficacy in ULT, this study is hypothesis-generating for the concept that depressive symptoms may be another factor that increases ULT noncompliance. These findings are consistent with a recent study of 125 Chinese patients with gout that linked poor ULT adherence with mental health problems (29). Studies with other patient populations (eg, with heart failure, diabetes, and hypertension) indicate that depressive symptoms reduce treatment adherence through low self-efficacy, or patients' beliefs that they cannot successfully comply with treatment (30–32), as well as other medication beliefs, such as greater perceived side effects and barriers to adherence, low motivation to perform the treatment, low perceived importance of treatment, and low expectations of treatment success (33,34). Importantly, intervention studies document that treating depression with psychotherapy or medication improves adherence in patients with HIV/AIDS and end-stage renal disease (35–38).

The present findings, if confirmed, could have important implications for research and clinical practice involving ULTs. First, the results suggest that clinical trials may underestimate treatment effects if they include participants with elevated depressive symptoms. Given the relatively high rates of major depression in the general population (7%-8% with recent depression) (39,40) and the well-established impact of depression on poor treatment adherence (16), initial studies of new treatments may benefit from screening for depressive symptoms and excluding participants with high levels of depression (eg, CESD-20 scores of 16 and above) to establish treatment effectiveness under "ideal conditions." Later trials may want to include participants with varying levels of depression to provide estimates of treatment effects that are more generalizable to the larger population.

Second, the results point to the utility of screening patients for depressive symptoms prior to prescribing ULTs and treating high levels of depression with cognitive behavioral therapy or antidepressants (41). This recommendation is particularly relevant given the increased risk for depression in patients with gout (20–23) and the crucial role of treatment adherence for effective management of hyperuricemia and gout (14,28). Brief validated screening measures for depression are now available, such as the two-item and nine-item versions of the Patient Health Questionnaire (PHQ-2 and PHQ-9) (42), the Hospital Anxiety and Depression Scales (43), and for older patients, the Geriatric Depression Scale (44). In fact, the US Preventive Services Task Force recommends all adults to be routinely screened for depression, with systems in place for diagnosis, treatment, and follow-up (45).

This study had multiple strengths, including a rigorous crossover randomized clinical trial design and use of a validated measure of depressive symptoms. Limitations included the relatively small sample size, which limited statistical power to detect smaller effect sizes. Although not all participants from the clinical trial had complete data to be included in this report, the included sample did not differ from those excluded on any baseline variables. The measurement of treatment adherence with measurable oxypurinol levels was also limited in its sensitivity to detect partial nonadherence and substantial missing data, but we believe that a strong objective end point conferred by the decrease in sUA supports the hypothesis of poor adherence to treatment. In addition, this clinical trial did not focus on patients with hyperuricemia or gout, so the present results should be replicated in these patient populations in future research. For instance, it is possible that despite depressive symptoms, patients with gout would be more motivated to adhere to treatment given the very

painful nature of this condition. Future studies should replicate the present findings using more rigorous measures of treatment adherence and in clinical care contexts (eg, by predicting treatment outcomes in patients with gout from depression levels). In conclusion, despite not involving patients with gout in whom the clinical implications would be more direct, this study provides the first evidence of an effect of depressive symptoms in the reduced efficacy of ULT in a clinical trial. Pending further confirmation in patients with gout, our findings support that patients who use ULTs and are not achieving treatment goals might need to be evaluated for depressive symptoms.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published. Dr. Gaffo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design. Mrug, Orihuela, Rahn, Saag, Gaffo. Acquisition of data. Rahn, Mudano, Foster. Analysis and interpretation of data. Mrug, Orihuela, Rahn, Mudano, Saag, Gaffo.

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