

QUETIAPINE AS COMBINATION TREATMENT WITH CITALOPRAM IN UNIPOLAR DEPRESSION WITH PROMINENT SOMATIC SYMPTOMS: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY

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SUMMARY

Background: Patients with major depressive disorder (MDD) accompanied by physical symptoms may be less responsive to antidepressant treatment. Quetiapine has been evaluated in the treatment of bipolar depression and has been recently approved as an add-on therapy for unipolar depression. Less is known about the efficacy of combination therapies in patients suffering from MDD with somatic symptoms. The aim of the present study was to evaluate the efficacy of quetiapine as adjunctive therapy to the SSRI citalopram in patients with MDD and somatic complaints.

Subjects and methods: 41 inpatients with nonpsychotic DSM-IV MDD experiencing significant symptoms of somatic distress as defined by a baseline score on the SCL-90-R somatization subscale greater one standard deviation above adult nonpatient norms were randomly assigned to receive either citalopram 40 mg/day plus placebo (n=20) or citalopram 40 mg/day plus quetiapine, 300 to 600 mg/day (n=21) for 6 weeks. The primary outcome measure was the Hamilton Depression Rating Scale (HDRS) score.

Results: Mean changes in HDRS scores from baseline to week 6 using last-observation-carried-forward methods were -12.3 ± 6.2 and -10.7 ± 5.1 in the citalopram-quetiapine and citalopram-placebo group, respectively. Remission rates were significantly higher in the citalopram-quetiapine-group (41.1%) than in the citalopram-placebo-group (26.3%), respectively.

Conclusions: Although quetiapine as add-on to citalopram did not separate statistically from placebo on the HDRS score in improving depressive symptoms and somatic symptoms in patients with MDD and prominent somatic complaints, higher remission rates and other second outcome parameters showed advantages for quetiapine. Larger, double-blind, placebo-controlled trials of quetiapine as augmentation therapy in MDD with somatic symptoms are warranted.

Key words: antidepressants – citalopram - major depression – quetiapine - somatic symptoms

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INTRODUCTION

Somatic symptoms are frequently encountered in patients suffering from major depressive disorder (MDD) (Corruble & Guelfi 2000). Such symptoms include, among others, sleep disturbance, fatigue, nonspecific musculoskeletal complaints and back pain. In clinical practice these symptoms are often disabling and significantly diminish quality of life in addition to the psychological symptoms of MDD. Furthermore, both somatic symptoms and pain predict a longer time to remission and are associated with more suicidality (Karp et al. 2005).

Somatic symptoms of MDD are underrepresented in standardized psychiatric rating scales and current psychiatric classification systems such as the DSM-IV. Therefore little is known about the relation between these symptoms and the “psychological” symptoms of

depression. This also holds true for the optimal treatment of patients suffering from MDD with multiple somatic complaints. This group of patients is still an especially difficult to treat one.

According to the World Health Organization (WHO), SSRIs constitute the first line treatment for MDD. Within this group citalopram has become very popular due to its efficacy and negligible drug-drug interactions (Brosen & Naranjo 2001). However, there is only a paucity of studies directly addressing the issue of MDD with somatic symptoms with any class of antidepressants. Tricyclic antidepressants have dual serotonin-/norepinephrine reuptake inhibition and are approved to reduce pain symptoms both in patients with and without MDD. Furthermore, the serotonin-/norepinephrine reuptake inhibitor (SNRI) duloxetine is approved for the treatment of MDD, diabetic peripheral neuropathic pain and fibromyalgia and it has been observed to improve

chronic pain in adults even without depression (Skljarevski et al. 2009). In another study, patients with MDD who were non- or partial-responders to SSRI treatment showed significant improvements in pain symptoms when switching to duloxetine (Perahia et al. 2009). On the other hand, the effects of SNRIs on somatic symptoms in depressed patients were not yet evaluated in patients primarily chosen for those symptoms in double-blind, placebo-controlled trials. Only in an open, randomized study, the SNRI venlafaxine and mirtazapine were investigated for somatic symptoms in MDD patients. Both antidepressants showed similar effects on efficacy and somatic symptoms in MDD patients (Kang et al. 2009). It is hypothesized that dual acting antidepressants have positive influences on pain because both serotonergic and noradrenergic neurons have been implicated in the mediation of endogenous pain inhibitory mechanisms via the descending inhibitory pain pathways in the brain and spinal cord (Millan 2002). However, also SSRI have effects on somatic symptoms. It is clinically well known that improvement of depressive symptoms also lead to improvements of somatic symptoms, but controlled trials are missing. In a study of Lin et al. depressed patients with pain symptoms showed improvements of both depression and pain after 6 weeks of treatment with fluoxetine, but the number of remitters was much smaller compared to depressed patients without pain symptoms (pain was a negative predictor for remission) (Lin et al. 2011).

The importance of somatic symptoms in MDD stems from the fact that the persistence of these symptoms might prevent patients responding to an antidepressant with complete resolution of all symptoms – the goal of any antidepressant treatment (Fava 2002). However, the practical clinical study STAR-D with the primary outcome of full remission who were first treated with one antidepressant (inclusive citalopram) revealed some disillusionizing results regarding this outcome parameter (Warden et al. 2007). Taken these findings together, current antidepressant treatment especially for physical symptoms in depressed patients is still limited. In case of treatment resistance, augmentation therapies with lithium, other antidepressants or atypical antipsychotics (AAP) have shown to be effective in several clinical trials. Olanzapine, aripiprazole and recently quetiapine are FDA-approved as add-on medication for treating depression. So far, none of the studies focused on the efficacy of combination therapies in patients suffering from MDD with somatic features. In a recent study, the active metabolite of quetiapine showed a strong inhibition of the norepinephrine transporter. One could assume that quetiapine together with a SSRI show similar effects like SNRIs on some somatic symptoms.

In our inpatient unit, specialized in the treatment of patients with severe affective disorders, we had found before in an open label fashion that adding quetiapine to

the antidepressant treatment regimen of patients with MDD and somatic symptoms may help achieve remission in hitherto only partially responsive patients. This motivated - together with the data from the literature - the start of this study.

In this pilot study we investigated whether the combination of citalopram/quetiapine would be superior to citalopram/placebo in terms of antidepressive effects and resolution of somatic symptoms in patients with somatic depression (MDD with somatic symptoms) after 6 weeks. To control effects of quetiapine on somatic symptoms, we conducted our study with citalopram to avoid additional direct effects on somatic symptoms from dual acting agents other than those of quetiapine.

SUBJECTS AND METHODS

Subjects

Inpatients with non-psychotic DSM-IV MDD experiencing significant symptoms of somatic distress were randomized to receive either citalopram (40 mg/day) plus placebo or citalopram (40 mg/day) plus quetiapine (300 to 600 mg/day) administered in a double-blind design for 6 weeks. From originally 41 screened patients (16 males, 25 females), 36 patients were randomized to the 2 groups. To prevent large imbalances in treatment group size a block randomization with blocks of four cases was used. The patients were recruited from the Department of Psychiatry and Psychotherapy of the Charité, University Medicine of Berlin, Campus Benjamin Franklin, and the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilian University, Munich, between November 1, 2004 and November 8, 2005.

We included subjects who were between 18 and 65 years old and met the DSM-IV criteria for MDD, current major depressive episode (MDE) (DSM-IV: 296.2; 296.3; ICD-10: F32.x; F33.x). The diagnosis of MDD based on the structured clinical interview for DSM-IV (SCID-I) (First et al. 1996) which was accomplished by the attending psychiatrists. All attending psychiatrists routinely took part in the weekly rater trainings for the Hamilton Depression Rating Scale (HDRS) and Montgomery-Åsberg Depression Rating Scale (MADRS) to ensure interrater reliability. Subjects must have had adequate fluency in German to complete baseline and follow-up interviews and able to fill out the “Hopkins Check List (HSCL)/(SCL-90)” (Derogatis et al. 1974). They needed to have a score of 2 on the HDRS item 13: “Somatic symptoms, general.” Furthermore, they had to score at least one standard deviation higher than the mean value of healthy controls on the subscale “somatization” of the “HSCL”/“SCL-90” (Schmitz et al. 2000) and must have been able to give written informed consent.

Subjects with any acute and/or life-threatening condition, such as collapse and shock, recent cardiac infarction and stroke, pregnant and breastfeeding women, women of childbearing potential who will not practice a medically accepted method of contraception and subjects who, in the investigator's judgement, posed a current significant suicidal or homicidal risk or patients who would not likely be able to comply with the study protocol were excluded. Moreover, subjects fulfilling the DSM-IV diagnostic criteria for current substance abuse and axis II disorder were excluded. Any antidepressant medication within one week before the first admission of the study medication constituted exclusion criteria. In case of fluoxetine this period was 5 weeks, in case of depot antipsychotics 3 months, in case of tranylcypromine 2 weeks. Any known contraindications to either citalopram or quetiapine and treatment with either citalopram or quetiapine during the current depressive episode were not allowed either.

Treatment

Quetiapine/placebo were started with 50 mg/day and titrated to 300 mg/day on day 4. After one week an increase – according to clinical judgement – up to 600 mg/day was possible. Every patient received citalopram. Citalopram was started with 20 mg/day and increased to 40 mg/day on day 3. Lorazepam was allowed as comedication at a dose of up to 3 mg/day. The mean dosage of the lorazepam used was a second outcome parameter. Treatment compliance was verified by the determination of plasma levels of quetiapine at week 2 and at the end of the study (week 6).

Efficacy and tolerability assessments

The primary outcome measure was the 17-item Hamilton Depression Rating Scale (HDRS) total score. Secondary outcome measures included the Montgomery-Åsberg Depression Rating Scale (MADRS) score, the self-reported Beck Depression Inventory (BDI) score, the SCL-90-R somatization subscale (SCL-90-R-s) score and the Clinical Impression Severity (CGI-S) and Improvement (CGI-I) scale scores. Primary and secondary outcome assessments were performed at baseline and weekly throughout the study. Response was defined as a reduction of least 50% of the initial HAM-D score and remission as an absolute score of less than 8 points.

Tolerability was measured by the Utvalg for Kliniske Undersøgelser (UKU) side effect rating scale (Lindgjaerde et al. 1987). Furthermore, a routine laboratory including complete blood count, liver enzymes, electrolytes, and creatinine was performed before randomization and every 2 weeks thereafter. Body weight was assessed before randomization, at week 2, week 4, and week 6. ECG recordings were performed at baseline and after 6 weeks. Blood pressure and heart rate were assessed weekly.

Statistical analysis

Sample size was determined in order to detect a difference of at least 4 points in HDRS-score after the treatment period with a power of 80% and at a significance level of 0.05. Statistical analyses were based on the intent-to-treat (ITT) principle with the last-observation-carried-forward (LOCF) approach applied for missing data. In a repeated-measures design changes in primary and secondary outcome parameters were compared between treatment groups, with primary and secondary outcome measures entered as within patient variables and factor treatment as between subjects variable (GLM, Repeated Measures Analysis of Variance). Group differences regarding baseline characteristics and mean changes between baseline and endpoint were analyzed using non-parametric Wilcoxon Two-Sample Test. All tests were performed with a double sided α -error $\alpha < 5\%$ ($p < 0.05$). The statistical analyses were performed by using SAS, version 9.1, software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Thirty-six (36) patients were randomized to citalopram/quetiapine ($n=19$) or citalopram/placebo ($n=17$).

There were no significant differences between treatment groups regarding baseline demographics like gender distribution, mean age, length of the actual episode, number of previous episodes, but mean HDRS-score with a numerical difference against the quetiapine group, which was not statistically significant (Table 1). However, there were no differences in the clinical characteristics of MDD between study completers and drop-out patients. The mean dosage of quetiapine was 310.0 mg daily, and the mean plasma level of quetiapine was 148.5 ng/ml ($SD \pm 39.88$). Although escalation up to 600 mg was theoretically possible, and far more frequently used in the placebo group. As a reason for this we assume that the placebo did not cause side effects as dizziness or somnolence and that patients in the placebo groups did not subjectively profit from lower “dosages”. On the other hand, it could be discussed that the higher dose escalation in the placebo group itself yielded in the high response rate in this group (placebo effect).

Efficacy

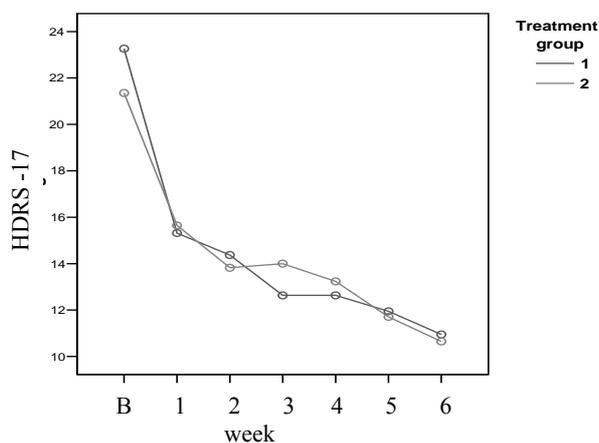
Repeated-measures analysis revealed a trend for a time x group interaction regarding changes in HDRS total score over 6 weeks ($F(6, 29) = 2.04, p=0.09$) with the combination of citalopram/quetiapine being superior to citalopram/placebo at Week 3 ($p=0.036$) of the study period. Treatment groups showed no significant time x group interactions with regard to changes in MADRS, BDI, SCL-90-R-s or CGI-S.

Table 1. Baseline characteristics of patients

	Citalopram + quetiapine (n=19)	Citalopram + placebo (n=17)
Age, mean (SD), years	45.1 (11.6)	48.4 (12.3)
Women, No. (%)	13 (61.9)	12 (60.0)
HDRS total score, mean (SD) range	23.3 (3.3) 18-29	21.4 (3.6) 12-27
Distribution of HDRS total scores, n (%)		
<18 points	1 (5.3)	3 (17.6)
18-24 points	11 (57.9)	11 (64.7)
>24 points	7 (36.8)	3 (17.6)
MADRS total score, mean (SD)	26.6 (5.9)	23.8 (6.4)
BDI score, mean (SD)	26.8 (7.3)	29.1 (10.9)
SCL-90-R somatization subscale score, mean (SD)	20.8 (10.1)	22.5 (6.2)
CGI-S score, mean (SD)	5.2 (0.6)	5.4 (0.6)
Duration of current MDE, mean (SD), months	5.8 (6.2)	4.7 (3.1)
Number of prior episodes of major depression, mean (SD)	5.3 (7.0)	3.4 (3.9)

SD, standard deviations; HDRS, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery Asperg Depression Rating Scale; BDI, Beck Depression Inventory; SCL-90-Rs, Symptoms Check List 90 Revised – Somatization Subscale; CGI-S, Clinical Global Impression of Severity; MDE, Major Depressive Disorder.

There were no statistically significant differences between treatment groups in mean change from baseline to the end of the study on the HDRS total score (Figure 1), or between group differences observed in mean change from baseline to week 6 on the MADRS, BDI, SCL-90-R-s and CGI-S and the mean CGI-I score at end point (Table 2). Focusing on somatic symptoms, no differences between the two groups could be detected (HDRS score item 13, SCL-90-R-s).



Treatment group: 1 = citalopram plus quetiapine, 2 = citalopram plus placebo. B: baseline. * = $p < 0.05$

Figure 1. HDRS total score over the study period (LOCF)

Analysis of mean changes from baseline to endpoint based on patients who completed the study by using the observed case approach showed a significant group difference in mean change from baseline in HAM-D total score favoring citalopram/quetiapine (mean (SD) change: citalopram/quetiapine (n=12): 15.50 (4.58) versus citalopram/placebo (n=13): 12.12 (4.28); ($p=0.04$)).

The mean daily dose of study medication (quetiapine/matching placebo) was significantly lower for quetiapine-treated patients compared with patients receiving matching placebo (mean (SD) daily dose: 310.00 (87.71) mg/day quetiapine vs. 533.33 (77.85) mg/day placebo; $p < 0.01$).

Mean changes in HDRS total scores from baseline to week 6 using last-observation-carried-forward methods were -12.3 ± 6.2 and -10.7 ± 5.1 in the citalopram/quetiapine and citalopram/placebo group, respectively. Higher remission rates were found in the quetiapine group (41.1% vs. 26.3%, respectively; $p < 0.02$).

The mean lorazepam dose in the citalopram/quetiapine group was 0.42 mg/day compared with 0.91 mg/day in the citalopram/placebo group ($p < 0.01$).

Tolerability

The combination of quetiapine and citalopram was generally well tolerated. 4 patients from the quetiapine group withdrew from the study during the first 3 days of treatment in the dose escalation period because of vertigo. This was noticed in a further 4 patients, therefore, the dose escalation phase was changed so that patients received quetiapine 50 mg/day in the first two days.

Sleepiness, constipation and orthostatic dizziness (hypotension) according to the UKU were the only side effects that occurred in more than 10% of the patients and more frequently in the quetiapine group. However, these side effects decreased over time and were only mild to moderate in severity (UKU scores of 1 to 2). There were no clinically relevant changes in heart rate, blood pressure, ECG parameters, EEG, routine laboratory or body weight in either group.

Table 2. Mean changes from baseline to endpoint (LOCF)

	Citalopram + quetiapine (n=19)	Citalopram + placebo (n=17)	p-value	Effect size η^2
Mean change in HAM-D total score (SD)	12.32 (6.16)	10.71 (5.06)	0.43	0.00
Percent change in HAM-D total score (SD)	47.99 (23.19)	49.06 (23.51)	0.97	
Response rate, n (%)	11 (57.89)	8 (47.06)	0.21	
Mean change in MADRS score (SD)	14.28 (10.95)	12.63 (6.28)	0.75	0.01
Mean change in BDI score (SD)	14.35 (8.85)	19.50 (11.20)	0.19	0.03
SCL-90-R-s, mean (SD)	11.94 (10.53)	15.43 (8.92)	0.25	0.02
Mean change in CGI-S score (SD)	-1.26 (1.24)	-1.35 (1.32)	0.88	
CGI-I score at endpoint, mean (SD)	2.16 (0.90)	2.12 (1.11)	0.80	

SD = standard deviation; HDRS, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery Asperg Depression Rating Scale; BDI, Beck Depression Inventory; SCL-90-R-s, Symptoms Check List 90 Revised – Somatization Subscale; CGI-S, Clinical Global Impression of Severity.

DISCUSSION

Both medication groups of this formerly difficult to treat population did surprisingly well regarding improvement of symptomatology in our study. Therefore, it was difficult to elicit an additional effect with quetiapine in this pilot study with only 36 patients. Nevertheless, this is to our knowledge the first placebo-controlled, prospective, randomized, double-blind study with quetiapine adjunctive treatment in patients with unipolar depression who experience prominent somatic symptoms. Also, to our knowledge, our study is the first one to evaluate quetiapine from the beginning of treatment and not as a sequential add-on.

Although quetiapine as add-on to citalopram did not separate statistically from placebo on the HDRS score in improving depressive symptoms in patients with MDD and somatic complaints in the ITT population, it did in the completer analysis. This difference between the two statistical methods result from the rather high drop-out rate (n=4) at the beginning of the study with the rapid augmentation of quetiapine that could be avoided by slower dose escalation. Moreover, apparent treatment induced side effects like vertigo, sleepiness, constipation and hypotension may have compromised the double-blind nature of the trial. Altogether, drop out rate was higher in the citalopram plus quetiapine group (n=7; 36.84%) compared to the citalopram plus placebo group (n=4; 23.53%). This difference in drop out rate can be explained by the rapid dose escalation of quetiapine at the beginning of the study which led 4 patients in the quetiapine group leave the study early (during the first 3 days of treatment) because of vertigo. Some numerical differences in response rates and second outcome parameters showed advantages for quetiapine, but the differences were statistically not significant. The fact, that in our studies significant differences in favour of quetiapine were found regarding remission but not response rates is not entirely clear. It also remains unclear, if quetiapine had specific effects on somatic symptoms or if the antidepressant

properties of quetiapine are responsible for the improvements of these symptoms. In a large study by Cookson et al. where data from BOLDER I and II were taken together to calculate numbers needed to treat in bipolar depression, both higher response and remission rates were found in the quetiapine groups (Cookson et al. 2007). However, these studies had no adjunctive design, what might have influenced the results.

Quetiapine has proven to antidepressant properties in different contexts, especially in bipolar depression (BOLDER I+II) (Calabrese et al. 2005, Thase et al. 2006). Moreover, it has shown to be helpful for treatment resistant depression (Dorée et al. 2007) where it also improves quality of sleep (Baune et al. 2007). In our sample lorazepam prescription was significantly lower in the quetiapine group, that might be a hint to less anxiety and sleeping problems in that group. Quetiapine has also shown to be effective in non-treatment resistant unipolar depression as add-on (McIntyre et al. 2007, Dannlowski et al. 2008, Bauer et al. 2009). Another study included patients who displayed comorbid anxiety and residual depressive symptoms (Garakani et al. 2008). Although somatic symptoms in patients with MDD occur frequently, none of these studies focused on that. Several studies showed positive effects on pain symptoms with antidepressants (SNRIs and tricyclic) in patients with MDD, but these effects could be attributed to the dual serotonin-/norepinephrine reuptake inhibition, but no controlled studies directly addressing the issue of MDD with somatic symptoms has been conducted so far with any class of antidepressants.

The mode of action of quetiapine that is involved in its antidepressant effect and its potentially positive effects on somatic symptoms are still under investigation. First, quetiapine is amongst other receptor binding profiles, a 5HT-2a antagonist, which per se could have been associated with antidepressant effects. Moreover, recent results suggest that norquetiapine, the major active human metabolite of quetiapine, has high affinity ($K_i=35$ nM) and is a potent inhibitor

(IC₅₀=13nM) of the norepinephrine transporter (NET) (Goldstein et al. 2007). Taken these modes of action together, one could assume that quetiapine has similar pharmacologic properties as dual acting antidepressants have. Additionally, in our study we have used a combination therapy together with citalopram, which probably also lead to serotonin-/norepinephrine reuptake inhibition. The main analgesic mechanism of action of antidepressants involves reinforcement of the descending inhibitory pathways by increasing the amount of norepinephrine and serotonin in the synaptic cleft at both supraspinal and spinal levels (Dharmshaktu et al. 2012). It has been observed that analgesic action is strongest in antidepressants with mixed receptor or predominantly noradrenergic activity (Salerno et al. 2002). Surprisingly, no differences in change of somatic symptoms could be detected. One could assume that even depressed patients with somatic symptoms profit by a monotherapy with a SSRI – maybe as a result of the antidepressive effect. To avoid ceiling effects, monotherapy with quetiapine should be evaluated against standard treatment (e.g. an SSRI and/or SNRI) and/or placebo.

The fact that the mean lorazepam dosage was lower in the quetiapine group may reflect the sedative properties of quetiapine in contrast to the placebo group. Moreover it can be assumed that quetiapine also has anxiolytic besides the well known antidepressant effects. On the other hand, the significant higher lorazepam dosage (0.91 mg/ day) in the placebo group versus 0.42 mg / day in the quetiapine group could also contribute to the high placebo response.

Limitations

Limitations of the study include the rather small number of patients. With this small sample size it is difficult to draw a solid conclusion. However, this study was meant to detect only clinically meaningful bigger effects, that could not be detected. Moreover, the combination treatment right from the start in contrast to an add-on design after only partial response and the rigid dose escalation regimen that might require adaptation in a real world scenario are further limitations. Indeed, drop out rate was higher in the citalopram plus quetiapine group compared to the citalopram plus placebo group, which might have affected the results. Furthermore, we did not control the effect of lorazepam on somatic symptoms, which possibly itself has positive effects on them.

In the light of our results we would suggest to use quetiapine in non-psychotic depression with somatic symptoms only up to 300 mg daily (perhaps even lower dosages like 100 mg daily are enough) and to increase the dose rather slowly in contrast to acute mania or schizophrenia (Smith et al. 2005, Leweke et al. 2007).

CONCLUSIONS

In this study, additional quetiapine to citalopram in patients with major depression and somatic symptoms did not show significant improvements regarding to the depressive symptoms and somatic symptoms. On the other hand, the remission rate was higher in the quetiapine group. Larger, double-blind, placebo-controlled trials of quetiapine as augmentation therapy in MDD with somatic symptoms are warranted.

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Conflict of interest:

Dr. Ion Angheliescu received a grant from AstraZeneca.

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