ORIGINAL RESEARCH

Impact of metoprolol treatment on mental status of chronic heart failure patients with neuropsychiatric disorders

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Background: Metoprolol treatment is well established for chronic heart failure (CHF) patients, but the central nervous system side effects are often a potential drawback.

Objective: To investigate the impact of metoprolol treatment on change in mental status of CHF patients with clinical psychological disorders (such as depression, anxiety, and burnout syndrome).

Methods: From February 2013 to April 2016, CHF patients with clinical mental disorders received metoprolol (23.75 or 47.5 mg, qd PO, dose escalated with 23.75 mg each time until target heart rate [HR] <70 bpm was achieved) at the Second Affiliated Hospital of Kunming Medical University. Mental status was assessed by means of the Hospital Anxiety and Depression Scale (HADS) and the Copenhagen Burnout Inventory (CBI) scale. The primary outcome assessed was change in mental status of patients post-metoprolol treatment and the association with reduction in HR achieved by metoprolol.

Results: A total of 154 patients (median age: 66.39 years; males: n=101) were divided into eight groups on the basis of their mental status. HR decreased significantly from baseline values in all the groups to <70 bpm in the 12th month, $P \leq 0.0001$. The HADS depression and CBI scores significantly increased from baseline throughout the study frame ($P \leq 0.0001$ for all groups), but a significant decrease in the HADS anxiety score was observed in patients with anxiety ($P \leq 0.0001$ for all groups). Regression analysis revealed no significant correlation in any of the groups between the HR reduction and the change in the HADS/CBI scores, except for a change in the CBI scores of CHF patients with depression ($P=0.01$), which was HR dependent.

Conclusion: Metoprolol treatment worsens the depressive and high burnout symptoms, but affords anxiolytic benefits independent of HR reduction in CHF patients with clinical mental disorders. Hence, physicians need to be vigilant while prescribing metoprolol in CHF patients who present with mental disorders.

Keywords: metoprolol, chronic heart failure, HADS anxiety and depression, high burnout, CBI scale, heart rate

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Introduction

Psychological disorders are common among patients with cardiovascular diseases. According to a literature review over the past decade, the prevalence rates of depression and anxiety among chronic heart failure (CHF) patients were 10%–60% and 11%–45%, respectively.[1] β blockers are widely used to treat CHF as several randomized clinical trials report their use to decrease hospitalizations and to enhance survival and well-being of heart failure (HF) patients.[2–7] However, earlier reports on the possible side effects of β blockers on the central nervous system (CNS), including the manifestation

of depression[8–12] and anxiety,[13] have placed β blockers on a controversial platform despite the well-established benefits. Cardiovascular researchers believe that peripheral effects of β blockers on the heart and kidneys lead to decreased chronotropy and inotropy, as well as lower blood pressure, all of which cause fatigue, decreased energy, and sexual dysfunction that may be interpreted as symptoms of new-onset depression.[14] A recent study by Burkauskas et al[15] reconfirmed the association between β blocker use and psychological function in patients with coronary artery disease. In contrast, Ranchord et al[16] reported that β blocker therapy was not associated with an increase in depressive symptoms in acute myocardial infarction patients. This discrepancy may be based on the individual β blocker used and its lipophilicity, as highly lipophilic β blockers are associated with the highest level of depressive symptoms.[17,18] On the other hand, although less research has been conducted on the association between the use of β blockers and symptoms of anxiety, few studies report anxiolytic benefits, especially with metoprolol.[19–21] However, these studies were not confined to patients with already existing clinical psychological disorders along with CHF. Recently, Brouwers et al[22] studied the antidepressant effects on cardiac function and mortality and reported that the use of antidepressants in HF patients is associated with increased risk of all-cause and cardiovascular mortality. Similarly, it is of paramount importance to inversely study the β blocker effects on changes in psychological behavior in HF patients, as earlier reports on adverse associations have potentially limited the use of β blockers in vulnerable patients. Furthermore, emotional stress due to depression or anxiety results in burnout syndrome manifested as fatigue and exhaustion. It is believed that burnout syndrome may be an overlap of depression or anxiety disorders.[23] A recent study reported a 4.1% prevalence of burnout syndrome and approximately 80%–90% stress among acute coronary syndrome patients.[24] However, the prevalence in HF patients has not been reported till date, yet it is plausible that a similar rate will be observed. Therefore, we prospectively investigated the impact of metoprolol (a moderately lipophilic β blocker) treatment on change in the mental status (depression, anxiety, and burnout syndrome) of CHF patients.

Methods

Study design

This is a prospectively designed single-center study executed from February 2013 to April 2016 using patients as their own controls. The protocol was approved by the Institutional Review Board of the Second Affiliated Hospital of Kunming Medical University and conformed to the Declaration of Helsinki and its subsequent revisions.

Selection of patients and grouping

CHF patients with resting heart rate (HR) >80 bpm and newly diagnosed with neuropsychiatric disorders such as depression and anxiety using the Hospital Anxiety and Depression Scale (HADS) questionnaire and high burnout status using Copenhagen Burnout Inventory (CBI) scores at the Second Affiliated Hospital of Kunming Medical University were included in the study. All the patients were included in the study only after obtaining a signed informed consent.

Certain categories of patients were excluded from the study. They included patients with bradycardia (resting HR <60 bpm), systolic blood pressure <90 mmHg, those who had used metoprolol in the recent 3 months, those with <6 months expected survival, pacemaker-dependent patients, those with contraindications to β blockers, those who were currently using Class I or Class III antiarrhythmic agents, tricyclic antidepressants, anxiolytics or any other CNS medications, and those who had undergone coronary bypass surgery or experienced a recent heart attack.

Treatment intervention and follow-up

Baseline data were collected from patients prior to treatment with initial 23.75 or 47.5 mg qd PO metoprolol continuous release tablets (Betaloc® ZOK; AstraZeneca, Södertälje, Sweden), and dose escalated in patients not responding to initial dose with 23.75 mg every 7 days until the target HR level (60–70 bpm) was achieved during follow-up. The average dose used to reach the target goal was 99.75 mg (47.5–142.5 mg). All patients were followed up at 1, 3, 6, and 12 months from intervention for final outcomes measurement.

Study outcomes

The primary outcomes were change in HADS depression and HADS anxiety scores along with CBI average scores in CHF patients with clinical psychiatric disorders post-metoprolol treatment in the 12th month. The secondary outcome was to evaluate the correlation between HR reduction and mental status.

HR measurement

Resting HR at baseline and 1, 3, 6, and 12 months post-metoprolol intervention was measured by electrocardiography after 3 minutes of rest.

Outcome assessment tools

The mental status of patients was assessed during each follow-up visit using HADS, which is a self-assessment scale (from 0 to 3 frequencies and scoring of 0–21 for each question) comprising 14 questions for evaluating the current severity of depression and anxiety. An average HADS score >7 represents the presence of anxiety or depression, with the highest score reflecting marked impairment.[25]

Burnout was measured using the CBI scale, which is a reliable and validated 19-item questionnaire to evaluate exhaustion and its attribution by the person using scales on personal burnout (6 items on physical and psychological exhaustion), work-related burnout (7 items attributed to exhaustion at work), and client-related burnout (6 items on exhaustion attributed to work with clients). In this study, only personal burnout was assessed, which had five response categories on a Likert scale, namely, "never", "seldom", "sometimes", "often", and "always". Each scale ranged from 0 to 100 points, with 100 indicating the highest level of burnout.[26]

Statistical analyses

All analyses were carried out on R (version 3.2.2) statistical software. Baseline characteristics are reported as descriptive data with counts, percentages, and mean ± standard deviation. Differences in HADS and CBI scores at different follow-up periods were compared with baseline using repeated measures one-way analysis of variance, followed by the post hoc Dunnet's multiple comparison test and χ^2 tests as appropriate. The Pearson correlation analysis was performed to estimate the association between mental status and HR reduction achieved with metoprolol. A P-value of <0.05 was considered statistically significant for all the analyses.

Results

Baseline characteristics

A total of 169 patients were included in the study, of whom 11 patients were excluded as they were intolerant to metoprolol dose increments and 4 patients were lost to follow-up. Finally, data of 154 patients (median age: 66.39 years; males [n=101], females [n=53]) were obtained in this study (Figure 1).

At baseline, the mean glomerular filtration rate was found to be 73.9±26.8 mL/min/1.73 m^2, and the mean body mass index was 23.85±3.62 kg/m^2. The majority of the patients were New York Heart Association Class III/IV (n=145, 94.15%), had a previous history of stroke (n=137, 88.96%) and hypertension (n=115, 74.67%), and were on

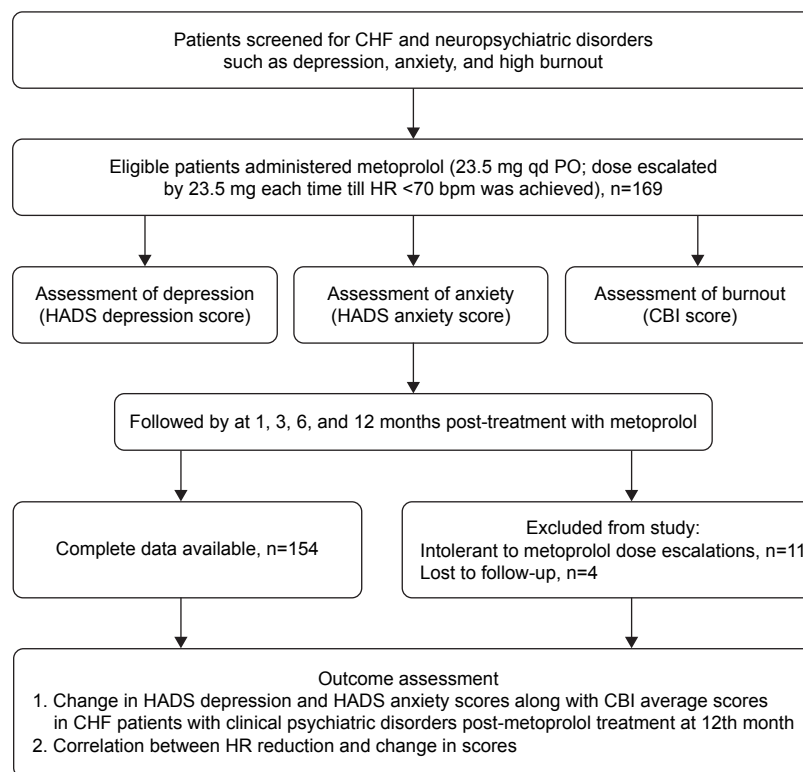**Figure 1** Study flowchart.
Abbreviations: CHF, chronic heart failure; HADS, Hospital Anxiety and Depression Scale; CBI, Copenhagen Burnout Inventory; HR, heart rate.

angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (n=149, 96.75%) and antithrombotic medication (n=146, 94.80%). None of the patients were on CNS medications (including anxiolytics and antidepressants). Details on the baseline characteristics are reported in Table 1.

Metoprolol-induced HR reduction

To assess the primary outcomes, patients were divided into eight groups on the basis of their mental status, as shown in Table 2. The average metoprolol dose required to reach the target HR goal was 99.75 mg. The average resting HR as measured by resting electrocardiogram decreased significantly from baseline values in all the groups to <70 bpm in the 12th month, $P<0.0001$ (Table 2).

Depressive effects of metoprolol

Metoprolol treatment was observed to result in a significant rise in the HADS depression score from baseline (10.00±0.20) at month 1 follow-up (10.76±1.78; $P \leq 0.05$), which remained stable through 12 months. The HADS depression score was highest in patients with both depression and anxiety (7.75±0.96 vs 13.70±1.40; $P \leq 0.0001$ compared to patients with only CHF) which remained stable throughout the study frame (13.64±2.20 vs 13.70±1.40, baseline vs 12th month). Although the HADS depression score was highest in patients with depression + anxiety + high burnout syndrome, the scores did not change post-metoprolol treatment. Depressive

Table 1 Baseline characteristics of overall patient population

Patient characteristics (n=154)	N (%)
Age, median years	66.39
Male	101 (65.58)
Female	53 (34.41)
Comorbidities	
Hypertension	115 (74.67)
Diabetes mellitus	101 (65.58)
Coronary artery disease	99 (64.28)
Stroke	137 (88.96)
Cardiac disease family history	54 (35.06)
Smoking	111 (72.07)
Alcohol	86 (55.84)
History of MI	59 (38.31)
BMI, mean (SD), kg/m²	23.85±3.62
GFR, mean (SD), mL/min/1.73 m²	73.9±26.8
NYHA Class III–IV	145 (94.15)
Concomitant medications at baseline	
ACEIs/ARBs	150 (97.40)
Diuretics	145 (94.15)
Digoxin	114 (74.02)
Antithrombotic agents	146 (94.80)

Abbreviations: MI, myocardial infarction; BMI, body mass index; GFR, glomerular filtration rate; NYHA, New York Heart Association; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Table 2 Heart rate changes after metoprolol treatment

Groups	Baseline	Month 12	P-value*
Depression (n=25)	83.48±7.46	64.68±3.44	<0.0001
Anxiety (n=15)	83.73±7.60	64.13±2.58	<0.0001
High burnout (n=16)	82.56±7.33	64.68±2.93	<0.0001
Depression + anxiety (n=17)	81.88±7.25	65.23±3.30	<0.0001
Anxiety + high burnout (n=21)	81.23±3.85	65.52±3.60	<0.0001
Depression + high burnout (n=15)	84.2±7.93	64.66±3.06	<0.0001
Depression + anxiety + high burnout (n=25)	82.04±5.36	64.64±3.43	<0.0001
Only CHF (n=20)	83.15±7.76	65.20±3.20	<0.0001

Notes: *χ^2 test. Data presented as mean ± standard deviation.
Abbreviation: CHF, chronic heart failure.

symptoms were significantly worsened in patients with depression and high burnout status at the 1st month follow-up and remained stable throughout the study frame (9.00±0.00 vs 12.93±1.48, baseline vs 12th month; $P \leq 0.0001$; Table 3).

Anxiolytic effects of metoprolol

In contrast to the depressive effects, metoprolol exerted positive effects in CHF patients with anxiety. At baseline, all the four groups with anxiety disorder had significantly high HADS scores compared with patients who had normal mental status (only CHF) ($P \leq 0.0001$ for all four groups). The HADS anxiety score significantly decreased from baseline in the 3rd month, which remained stable through the 6th and 12th months of follow-up ($P \leq 0.0001$ for all four groups; Table 3).

High burnout status post-metoprolol treatment

At baseline, patients with high burnout had high CBI average scores compared to patients with normal mental status ($P \leq 0.0001$ for all four groups). The burnout score increased significantly from baseline post-metoprolol treatment in the 3rd month, which remained stable through 12 months ($P \leq 0.0001$ for all four groups). However, a significant increase in CBI score was observed even at the 1st month follow-up period in patients with anxiety + high burnout (66.47±0.90 vs 68.05±3.56; $P=0.055$) and depression + high burnout (66.67±0.00 vs 68.89±3.81; $P=0.032$), indicating worsening of burnout syndrome (Table 3).

Correlation of HR reduction with change in mental status

Regression analysis to study the impact of HR reduction by metoprolol on change in mental status revealed no significant correlation in any of the groups between HR reduction and change in HADS/CBI scores. However, change in the CBI

Table 3 Change in mental status post-metoprolol treatment

Groups	Baseline	Month 1	Month 3	Month 6	Month 12
HADS depression average scores					
Depression	10.00±0.20	10.76±1.78*	10.92±1.77*	10.92±1.77*	10.88±1.69*,#
Anxiety	–	–	–	–	–
High burnout	–	–	–	–	–
Depression + anxiety	13.64±2.20	13.82±1.59	13.88±1.40	13.76±1.43	13.70±1.40#
Anxiety + high burnout	–	–	–	–	–
Depression + high burnout	09.00±0.00	12.00±2.61**	12.53±2.13**	12.46±2.13**	12.93±1.48**,#
Depression + anxiety + high burnout	11.56±0.50	11.68±0.69	11.68±0.69	11.68±0.69	11.56±0.50#
Only CHF	06.05±0.22	07.25±1.48	07.25±1.48	07.45±1.46	07.75±0.96
HADS anxiety average scores					
Depression	–	–	–	–	–
Anxiety	10.80±1.51	10.46±1.50	08.40±0.82**	08.26±0.79**	07.73±0.79**,#
High burnout	–	–	–	–	–
Depression + anxiety	10.23±1.52	10.17±1.46	08.00±0.79**	07.88±0.78**	07.64±0.60**,#
Anxiety + high burnout	09.76±0.43	09.71±0.46	07.38±0.58**	07.38±0.58**	07.80±0.81**,#
Depression + high burnout	–	–	–	–	–
Depression + anxiety + high burnout	09.56±0.50	09.48±0.50	07.68±0.80**	07.52±0.65**	07.80±0.57**,#
Only CHF	06.55±0.82	06.50±0.82	06.50±0.82	06.6±0.82	06.25±0.63
CBI average scores					
Depression	–	–	–	–	–
Anxiety	–	–	–	–	–
High burnout	66.67±0.00	66.67±0.00	68.75±3.72*	68.75±3.72*	71.19±3.23**,#
Depression + anxiety	–	–	–	–	–
Anxiety + high burnout	66.47±0.90	68.05±3.56*	70.63±4.26**	70.63±4.26**	70.83±2.94**,#
Depression + high burnout	66.67±0.00	68.89±3.81*	70.55±4.30***	71.11±4.30***	71.77±2.81**,#
Depression + anxiety + high burnout	64.33±2.11	65.33±2.87	70.16±4.91**	70.16±4.91**	68.00±5.60****,#
Only CHF	50.41±1.86	50.41±1.86	50.41±1.86	50.41±1.86	52.50±2.83

Notes: *$P \leq 0.05$, **$P \leq 0.0001$, ***$P \leq 0.001$, ****$P \leq 0.01$: compared to baseline values; #$P \leq 0.0001$: compared to values of only CHF group.
Abbreviations: HADS, Hospital Anxiety and Depression Scale; CHF, chronic heart failure; CBI, Copenhagen Burnout Inventory.

scores in patients with depression was significantly (P=0.01) associated with reduction in HR (Table 4). The mechanistic study and validation are warranted in future studies.

Discussion

In the present study, we examined the impact of metoprolol treatment on the mental status of CHF patients. The study findings do not support an association between metoprolol

Table 4 Correlation between HR reduction and change in mental status in 12th month

Groups	HADS depression[a]	HADS anxiety[a]	CBI[a]
Depression	0.32	0.07	0.01
Anxiety	0.55	0.48	0.94
High burnout	0.82	0.06	0.78
Depression + anxiety	0.55	0.21	0.15
Anxiety + high burnout	0.62	0.61	0.67
Depression + high burnout	0.74	0.26	0.40
Depression + anxiety + high burnout	0.90	0.92	0.52
Only CHF	0.63	0.49	0.39

Note: [a]P-values for regression analysis coefficients.
Abbreviations: HR, heart rate; HADS, Hospital Anxiety and Depression Scale; CBI, Copenhagen Burnout Inventory; CHF, chronic heart failure.

use and symptoms of anxiety or depression in CHF patients as these aspects have been extensively studied in previous literature.[17,19–21] However, there is no evidence on the impact of metoprolol treatment on mental status in CHF patients with clinically diagnosed depression or anxiety disorder. In addition, to the best of our knowledge, this study is the first to investigate the impact of metoprolol treatment on burnout status in CHF patients.

Patients with CHF have clinically significant depression and anxiety two- to three fold higher than that of the general population with a prevalence of 30%–50%,[27–29] and thereby present a potential challenge in successful CHF treatment. Unfortunately, depression and anxiety go unrecognized while diagnosing and prescribing medications to treat CHF owing to the overlap of CHF symptoms such as fatigue, poor sleep, and weight changes with depressive symptoms such as insomnia and psychomotor retardation.[30] The treatments intended for CHF may impose side effects on CNS, thereby worsening or improving the mental status. Studies have found that β blockers have to be lipophilic and able to cross the blood–brain barrier to exert neuropsychological side effects.[31] Metoprolol, a moderately lipophilic β blocker commonly

prescribed for CHF, also prevents a part of pressor response to psychological stress.[32] Studies suggest that depression is associated with a poor prognosis of survival in CHF patients, and antidepressant treatment has shown only modest or no improvements in outcomes.[33] Furthermore, randomized trials have shown failure of nonpharmacologic strategies in the treatment of depression in CHF patients.[34,35] Hence, there is paucity of data on safe and efficacious treatment of depression with HF. This study finding further suggests that use of metoprolol in the treatment of CHF rapidly worsens the existing depressive symptoms in CHF patients. However, the mechanism by which metoprolol worsens depression is unclear. We tried to correlate the reduction in HR by metoprolol with the change in mental status and found no correlation between the indices, explaining HR independent effects on CNS. It is just assumable that CHF patients are likely to take other drugs such as antihypertensives or antiarrhythmic drugs, which may explain the side effects of metoprolol as a consequence of pharmacokinetic interactions.[36] One more hypothesis may be the role of metabolizing enzymes, as studies report high adverse events of metoprolol in patients with low CYP2D6 activity.[37] Hence, the use of metoprolol in CHF patients with depression must be cautiously chosen, and future studies are warranted to study the effect of combined antidepressant and β blocker therapy on outcomes in CHF patients with depression. This study is confined to elderly CHF patients who often present with comorbid diseases such as depression and anxiety.[38]

Anxiety has been related to the increased incidence of sudden death in patients with CHF.[39] Animal studies indicate that β-1 selective adreno-receptors (b1-AR) in basolateral amygdala mediate anxiety-like behavior and that inhibition of these receptors by b1-AR blockers could produce anxiolytic effects.[19] Further research on human subjects has proved the anxiolytic effects of a β-1 selective adrenergic blocker, metoprolol.[20,21] However, whether this benefit is translated in CHF patients with anxiety remains obscure. From our investigation, we report rapid and significant improvement of anxiety disorder, suggesting anxiolytic benefits of metoprolol in CHF patients. Furthermore, emotional stress due to depression or anxiety results in burnout syndrome manifested as fatigue and exhaustion. It is believed that burnout syndrome may be an overlap of depression or anxiety disorders.[23] For the first time, we attempted to study the impact of metoprolol treatment on burnout status of CHF patients and found that metoprolol significantly worsens the already existing high burnout. Although our study shows small differences in statistical significance, the representativeness of clinical

significance is questionable owing to the very small sample sizes of groups, which is majorly due to enrollment at a single-center design where the number of patients with HF who received metoprolol was limited and not all patients agreed to provide informed consent for this study. However, of note, baseline was very balanced among the majority of the patients. Hence, we are confident that there were no baseline differences in HF severity and mental status that would have biased the comparison between the groups. Also, previous studies of Cucchini et al,[40] Eichhorn et al,[41] and de Figueiredo Neto et al[42] used a population of similar size to elucidate the cardiovascular effects of metoprolol in patients with cardiovascular diseases. These studies indicate that a sample size of 15–20 patients might be sufficient to translate the findings to clinically significant data. However, large-sized studies may be warranted to prove our evidence right.

Overall, we suggest that depression, anxiety, and burnout status must be recognized in CHF patients prior to prescribing metoprolol by improving the sensitivity of mental health screening. However, the findings of this study should be interpreted cautiously as the study is limited by a number of factors. The small sample size may not be adequately powered to conclude the findings, warranting future large-size studies. Furthermore, the role of antidepressants on metoprolol-induced changes in mental status was not studied, which is very important as antidepressant therapies themselves do not benefit cardiac outcomes, and metoprolol effects may vary in their presence. We used a study design that could not assess the cause of the effect, and long-term effects of β blockers on mental status remain unclear. Also, the impact of changed mental status on cardiac outcomes is obscure, warranting further investigation. Furthermore, we relied on self-report measures to assess anxiety and depression rather than a clinical diagnostic interview. It is likely that many patients may not have accurately reported their mental status or may have been overlooked by the investigators. However, the HADS was specifically designed to avoid false positives when administered in hospital settings and therefore focuses on psychological and cognitive symptoms rather than somatic symptoms or sleep and appetite disturbance.[43] Furthermore, the tools have standardized and validated psychometric properties in Chinese patients, ensuring reliable assessment.[44,45] Finally, we assumed that the metoprolol effects were mediated through the reduction in HR, and hence we studied the correlation between HR reduction and mental status without adjusting for general confounders such as age, gender, CHF severity, and so on. Hence, further studies need to investigate the correlation of

all the associated factors of metoprolol treatment with the changes in mental status, and this study finding may provide a preliminary report on the possible outcomes.

Conclusion

Metoprolol treatment significantly worsens the depressive and high burnout symptoms, but affords anxiolytic benefits independent of HR reduction in CHF patients with clinically diagnosed mental disorders. Hence, physicians need to be vigilant with regard to the potential presentation of mental disorders in CHF patients while prescribing metoprolol.

Author contributions

All authors contributed equally to the study and development of the manuscript. YM and XL conceptualized and designed the study. XL and XC were involved in data collection and analysis. All authors contributed toward data analysis, drafting, and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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