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Hyperinsulinaemia associated with β-adrenoceptor antagonist in medicated bipolar patients during manic episode ☆

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Abstract

Hyperinsulinaemia, a pre-clinical condition which is considered to predict insulin resistance and metabolic syndrome, has not been sufficiently investigated in bipolar disorder, despite evidence to suggest that bipolar patients are at risk of developing insulin resistance. This study was set out to determine the alteration in fasting insulin levels and evaluate the factors associated with hyperinsulinaemia during manic episodes. Measurements were taken of the fasting plasma insulin and leptin levels, as well as the body mass index (BMI), amongst 42 physically healthy bipolar I manic (DSM-IV) patients aged ≤45 with Young Mania Rating Scale (YMRS) scores of ≥26. These were then compared with their values in subsequent remission (YMRS ≤12). A total of 14 patients (33.3%) in acute mania and 30 patients (71.4%) in subsequent remission met the Taiwanese criteria for hyperinsulinaemia of ≥8.7 μIU/ml for men, and ≥11.3 μIU/ml for women. Multiple analyses were then undertaken, without correction, as the exploratory analyses. The measurement, by logistic regression, of the use of propranolol in remission (odds ratio [OR]=10.04, 95% confidence interval [95% CI]=1.03–97.96) and the increase in BMI (OR=1.35, 95% CI=1.01–1.80) were found to have independent associations with hyperinsulinaemia in subsequent remission. Our results suggest that medicated bipolar manic patients are vulnerable to hyperinsulinaemia in early remission, particularly those gaining bodyweight or those using β-adrenoceptor antagonist (beta-blockers), irrespective of the types of mood stabilizers or antipsychotics used.

Keywords: Beta-blocker; Bipolar I disorder in Taiwan; Bodyweight gain; Hyperinsulinaemia; Insulin resistance; Manic episode

1. Introduction

Hyperinsulinaemia has been found to be closely linked to overall and central obesity, impaired glucose regulation and metabolic syndrome (Reaven, 1988; Jensen and Collazo-Clavell, 2004). The prevalence of obesity, metabolic syndrome and its sequels (cardiovascular diseases and diabetes mellitus) is known to be elevated in patients with bipolar disorder, particularly those receiving the novel psychopharmacological therapy (Fagiolini et al., 2005; McIntyre et al., 2005; Tsai et al., 2005).

Although the adverse effects of β-adrenoceptor antagonists (beta-blockers) on lipid and carbohydrate metabolism have already been well documented (Kaplan, 1992), beta-blockers, such as propranolol, have been widely used in bipolar patients as a means of alleviating the problematic tremors associated with lithium and valproate, as well as the extra-pyramidal syndrome induced by antipsychotics (Holloman and Marder, 1997).

A state-dependent activation of the immunomodulatory system in bipolar mania was demonstrated in our earlier works (Tsai et al., 1999, 2001). Furthermore, bipolar disorder has also been shown to be associated with increased production of pro-inflammatory cytokines, such as interleukin-8 and tumor necrosis factor (TNF)-alpha, both in the manic and depressed phases, as compared to the levels found in healthy subjects (O'Brien et al.,

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2006). Leptin, the adipose tissue-derived hormone, plays an important role in triggering the adaptive response to starvation since weight loss causes leptin levels to fall in proportion to the loss of body fat (Flier, 1998). Pro-inflammatory cytokines and leptin are key agents in the linkage between inflammation, insulin insensitivity and disturbances in lipid metabolism. This is particularly so for TNF-alpha, which is a product of adipocytes as well as cells of the immune system (Grimble, 2002).

Taken together, patients with bipolar disorder may represent an at-risk group for both glucose metabolic abnormalities (McIntyre et al., 2005) and insulin resistance. Racial differences may also be present in the clustering of insulin resistance syndrome (Saad et al., 1991); however, there is currently only limited data available on the production of insulin and leptin during manic episode in bipolar patients, particularly in terms of reports from non-Western populations. The measurement of fasting insulin has been recommended as a surrogate estimate of insulin resistance (Balkau and Charles, 1999). Individuals with bipolar disorder are at risk of obesity as well as metabolic syndrome, with increased adiposity being associated with increases in circulating leptin level and insulin resistance. Hence, it is hypothesized that hyperinsulinaemia tends to exist in bipolar manic patients, particularly those who receive beta-blockers and gain bodyweight. This study consequently represents an attempt to evaluate the prevalence of hyperinsulinaemia during manic episodes in bipolar disorder patients, and to investigate the associated factors, including the alteration in leptin levels.

2. Methods

2.1. Subjects

Patients meeting the DSM-IV diagnostic criteria for bipolar I disorder, aged ≤45 years with Young Mania Rating Scale (YMRS) scores of ≥26 (Young et al., 1978), were invited to participate in the study. These patients were rated and diagnosed by two senior psychiatrists using the Chinese version of the Structured Clinical Interview for DSM-III-R, patient edition (Spitzer et al., 1990). Written informed consent was required from all subjects agreeing to participate in the study. Patients were subsequently screened by physical examination, with complete blood counts (with differentials), serum enzyme and metabolite screening, and thyroid function tests also being carried out. The exclusion criteria included the presence of any severe physical illness, any history of alcohol/substance abuse, any prior history of lipid lowering treatment and the presence of any endocrinological state. Patients with mixed episodes, or any other Axis I psychiatric disorders, were also excluded. Follow-up blood samples of the same manic patients were collected whilst in subsequent remission (YMRS scores ≤12 and Hamilton Depression Rating Scale [HDRS-21] ≤8).

For mania of all types, the first-line options were mono-therapy with lithium or valproate alone, and then a combination of antipsychotics with either lithium or valproate was considered. The dosage for both mood stabilizers was determined clinically, based upon their effectiveness and the tolerability of the patients. Severely ill or overactive patients may require short-term adjunctive treatment with a benzodiazepine. The use of beta-blockers (propranolol) was also considered for lithium tremor and antipsychotic-induced akathisia.

2.2. Assays

Heparinized blood was drawn by venous puncture following an overnight fasting from 2400 h of the preceding night. Plasma was collected and frozen at −80 °C until use. Assays of insulin and leptin in bipolar individuals, during both acute mania and remission, were carried out simultaneously, and in the same run. The respective intra-and inter-assay coefficients of variation (CV) were <7% for leptin and <12% for insulin.

The reference range for normal fasting insulin was 2.1 to 30.8 μIU/ml, with hyperinsulinaemia being defined by the top quartile cut-off for fasting insulin, specified by gender, in the non-diabetic background Taiwanese population: ≥8.7 μIU/ml (52.45 pmol/l) for men, and ≥11.3 μIU/ml (67.84 pmol/l) for women (Chien et al., 1999).

2.3. Statistical analysis

Prior to the analysis, the data were evaluated for normality of distribution using Levine's test. Differences in the continuous variables between acute mania and subsequent remission in bipolar individuals were assessed by means of the paired-*t* test. Two-group comparisons were then undertaken. The Chi-square test or Fisher's exact test was used for the categorical variables, including gender, previous history of depressive episode, smoking, use of propranolol and co-existing psychotic features, whilst the *t*-test was used for the continuous variables, including age, age at onset, number of prior affective episodes, time interval between acute and remission measurements, daily dosage of lithium and valproate, chlorpromazine (CPZ) equivalent (mg/day) and BMI.

Pearson's product-moment correlations were then used to examine the relationship between the continuous variables. Given the exploratory nature of this study, the univariate analyses are presented without Bonferroni corrections. The relevant variables found to be significant in the univariate analyses were selected for entry into a multivariate logistic regression using SPSS Base 10.0 software, so as to investigate the contribution of the clinical variables to hyperinsulinaemia. Any independent variables with at least a potentially moderate

Table 1
Comparison of insulin, leptin, body weight and body mass index between acute mania and subsequent remission of bipolar patients (N=42)

Variables	Acute mania		Subsequent remission		*t*	*p*-value
	Mean	S.D.	Mean	S.D.		
Insulin, μIU/ml	11.14	14.39	48.27	51.39	3.71	<0.001
Leptin, ng/ml	15.02	15.01	20.81	17.14	2.86	<0.01
Body weight, kg	64.60	12.87	67.10	12.84	3.62	<0.001
Body mass index, kg/m^2	24.0	4.1	24.9	4.1	3.63	<0.001

Table 2
Comparison of clinical features between propranolol and non-propranolol groups in subsequent remission

	Propranolol group (N=16)	Non-propranolol group (N=23)	p-value
Age, years [a]	33.1±9.8	33.7±7.5	ns
Male [b]	9 (56.3%)	12 (52.2%)	ns
Smoking habit [c]	6 (37.5%)	4 (17.4%)	ns
Dosage of typical antipsychotics [a] (CPZ equivalent/day)	145.0±198.6	133.87±242.8	ns
Change in BMI [a], kg/m^2	1.1±0.6	0.7±0.5	ns

[a] t-test.
[b] Chi-square test.
[c] Fisher's exact test.

association with hyperinsulinaemia (p<0.1) were selected for entry into the multivariate logistic regression model.

3. Results

3.1. Demographic and clinical characteristics

The manic patients participating in this study comprised of 20 females and 22 males with a mean age of 33.1±8.5 years and a mean age at onset of 23.9±7.1 years. The mean time interval between the measurements in acute mania and the measurements in subsequent remission was 46.2±28.4 days, ranging between 12 and 116 days, whilst the mean length of the index episode was 61.6±39.0 days. The plasma insulin and leptin levels, bodyweight and BMI were all significantly elevated in subsequent remission (Table 1).

3.2. Patients with hyperinsulinaemia

In acute mania, 14 patients (33.3%) met the Taiwanese criterion for hyperinsulinaemia and four patients (7.1%) had abnormally high fasting insulin levels (>30 μIU/ml). In subsequent remission, the numbers of hyperinsulinaemic patients were elevated, with 30 patients (71.4%) fulfilling the Taiwanese hyperinsulinaemic criteria and 20 (47.6%) displaying abnormally high insulin levels. In accordance with the Western definition for hyperinsulinaemia (Després et al., 1996; Ferrannini and Balkau, 2002), more patients with fasting insulin levels greater than 15 μIU/ml were found in subsequent remission (N=26, 61.9%) than in acute mania (N=10, 23.8%).

Those patients fulfilling the Taiwanese criterion for hyperinsulinaemia in subsequent remission included 93.8% of the 16 patients taking propranolol and 57.7% of the 26 patients who were free of propranolol during the manic episode. However, there were no differences in the mean plasma insulin levels at the baseline measurements in acute mania amongst the drug-free patients (N=9, 10.47±8.54 μIU/ml), the medicated patients free of propranolol (N=20, 11.32±11.83 μIU/ml), and the propranolol-treated patients with a mean daily dosage of 21.0 mg (N=13, 11.33±20.90 μIU/ml).

3.3. Patients taking propranolol and propranolol-free patients

At the follow-up measurement in subsequent remission, the 16 patients taking propranolol with mean daily dosage of 34.6 mg were classified as the propranolol group. Three patients who had been taking propranolol at acute measurement discontinued the use of such drug prior to remission state.

The remainder of the patients did not receive propranolol throughout the manic episode (N=23) and were classified as the non-propranolol group. There were no significant differences in demographic data, smoking habit, change in BMI or daily dosage of typical antipsychotics between the propranolol and non-propranolol groups (Table 2).

However, as compared to their values at acute measurement, in subsequent remission, the mean plasma insulin levels and mean BMIs of these two groups were significantly elevated (Table 3). Furthermore, within the propranolol group, there was no significant statistical difference between the mean leptin levels in acute mania (20.56±20.09 ng/ml) and in remission (24.78±15.63 ng/ml, paired-t=−1.32).

In acute mania, the mean length of propranolol usage for all 42 patients was 4.3±19.7 days, with a mean daily dosage of 11.3±6.0 mg; in subsequent remission the mean length of use was 12.3±27.5 days, with a mean daily dosage of 10.7±22.5 mg. Pearson's product-moment correlations showed that for all of the patients, only the propranolol daily dosage had positive correlation with the insulin level in subsequent remission (γ=0.465, p<0.0025); however, since 54.8% of the patients had not taken propranolol throughout their entire episode, this variable was not included within the regression equation. Furthermore, neither the length of exposure to propranolol nor the total dosage prior to the measurement had any significant relationship with insulin levels in both the acute and remission phases (data not shown).

Table 3
Comparisons between fasting insulin levels and BMI for propranolol and non-propranolol treated bipolar disorder patients

	Propranolol group (N=16)		Comparison, p	Non-propranolol group (N=23)		Comparison, p		
	Acute mania [A]	Remission [B]	A *vs.* B	Acute mania [C]	Remission [D]	C *vs.* D	A *vs.* C	B *vs.* D
Insulin, μIU/ml	12.71±20.16	67.50±52.22	<0.001 [a]	11.15±9.84	26.18±30.69	<0.025 [b]	ns	<0.005 [c]
BMI, kg/m^2	24.1±4.4	25.3±4.2	0.025 [d]	23.9±4.1	24.7±4.2	0.001 [e]	ns	ns

[a] Paired-t=4.28, df=15.
[b] t=2.52, df=22.
[c] t=3.11, df=37.
[d] Paired-t=2.82, df=15.
[e] t=3.91, df=22.

Table 4
Comparison between continuous variables of bipolar patients with and without hyperinsulinaemia in subsequent remission

Variables	Patients with hyperinsulinaemia (N=30)	Patients without hyperinsulinaemia (N=12)	t	p-value
	Mean (SD)	Mean (SD)		
Age, years	32.9(8.4)	33.7(9.2)	0.27	ns
Age at onset, years	23.1(7.2)	25.8 (6.5)	1.13	ns
No. of lifetime affective episodes	4.9 (4.0)	5.2 (4.2)	0.16	ns
Lithium dosage in remission, mg/day	555.2 (611.0)	350.0 (418.9)	−1.23	ns
Valporate dosage in remission, mg/day	646.7 (635.0)	600.0 (668.8)	−0.21	ns
Time interval between acute and remission measurements, day	40.2 (19.0)	47.0 (30.4)	0.57	ns
Insulin level in acute mania, μIU/mL	12.27 (15.96)	8.32 (9.39)	−0.80	ns
Insulin level in remission, μIU/mL	57.06 (44.59)	5.31(3.73)	−6.30	<0.001
BMI in acute mania	24.5 (4.3)	23.6 (3.9)	−0.59	ns
BMI in remission, kg/m^2	25.7 (4.2)	22.5 (2.9)	2.27	<0.025
Leptin level in acute mania, ng/mL	14.1 (12.90)	17.3 (19.83)	0.61	ns
Leptin level in remission, ng/mL	23.59 (18.68)	13.89 (10.02)	2.18	<0.05

3.4. Relationship between leptin, insulin, body weight, BMI and time to remission

In acute mania, the BMI had a significantly positive relationship with leptin level (Pearson's product-moment correlations: r=0.38, p<0.025), but no relationship was found between insulin levels and the BMI or leptin levels (data not shown). In subsequent remission, the insulin level had a significantly positive relationship with both leptin level (Pearson's product-moment correlations: r=0.43, p<0.005) and BMI (Pearson's product-moment correlations: r=0.53, p<0.001).

The elevation of plasma leptin levels from the baseline in acute mania to the follow-up measurements in remission (Δleptin; endline values minus baseline values) had a significantly positive correlation with the increase in BMI (ΔBMI; Pearson's product-moment correlations: r=0.32, p<0.05) and the increase in bodyweight (ΔBW; Pearson's product-moment correlations: r=0.27, p=0.067). However, the Δinsulin had no correlation with Δleptin, ΔBMI or ΔBW (data not shown). There was no significant relationship between time to remission and the BMI value, and the insulin or leptin levels in subsequent remission (data not shown).

3.5. Medication status

At the baseline measurement in acute mania, there were a total of eight patients (19.0%) taking lithium alone with a mean daily dosage rate of 862.5±244.9 mg and further eight patients (19.0%) taking valproate alone with a mean daily dosage of 1028.6±298.4 mg. Each patient was treated with at least one mood stabilizer throughout the period of their acute episode, including lithium (N=14, 33.3%), valproate (N=19, 45.2%) and lithium plus valproate (N=9, 21.4%).

The follow-up measurements in subsequent remission showed that the mean daily dosage for those receiving lithium (N=20, 47.6%) was 1047.4±315.1 mg, whilst the mean dosage for valproate was 1195.2±247.9 mg (N=22, 52.4%). The follow-up measurements in subsequent remission also showed that 11 patients had received concomitant medication with atypical antipsychotics (clozapine, N=7; olanzapine, N=1; quetiapine, N=3) at a mean of 290.0±258.5 CPZ equivalent/day. At the baseline measurement in acute mania, six of these patients were on atypical antipsychotics (clozapine, N=2; quetiapine, N=2; olanzapine, N=2) with a mean of 315.3±362.0 CPZ equivalent/day, and three had been on antipsychotics (clozapine, N=2; quetiapine, N=1) prior to entering the study.

In subsequent remission, there was no difference between the mean insulin level of patients medicated with atypical antipsychotics (N=11, 41.06±48.63 μIU/ml) and that of the rest of patients (49.88±53.20 μIU/ml), including ten patients

Table 5
Comparison between categorical variables of bipolar patients with and without hyperinsulinaemia in subsequent remission

Categorical variables	Patients with hyperinsulinaemia (N=30)		Patients without hyperinsulinaemia (N=12)		p-value
	N	%	N	%	
Male	19	63.3	3	25.0	<0.05
Prior history of depressive episode	6	20.0	5	41.6	ns
Without co-existing psychotic feature	4	13.3	1	8.3	ns
Smoking	11	36.6	0	0	<0.025
Medication through the index episode					
Any use of atypical antipsychotics	4	13.3	2	16.7	ns
Lithium alone	10	33.3	4	33.3	ns
Valproate alone	12	40.0	2	16.7	ns
Use of propranolol					
In acute mania	12	40.0	1	8.3	0.067
In subsequent remission	15	50.0	1	8.3	<0.025

By Fisher's exact test.

taking mood stabilizers alone and the 21 patients receiving concomitant typical antipsychotics ($t=1.05$, $df=40$, ns).

3.6. Factors associated with hyperinsulinaemia

Comparisons in subsequent remission between the hyperinsulinaemic (mean insulin level 57.06±44.59 μIU/ml) group and the non-hyperinsulinaemic (mean insulin level 5.31±3.73 μIU/ml) group are provided in Tables 4 and 5.

Based upon the univariate associations identified in Tables 4 and 5, the multivariate logistic regression revealed that the use of propranolol in remission (adjusted OR=10.04; 95% CI=1.03–97.96) along with the increase in BMI (adjusted OR=1.35; 95% CI=1.01–1.80) provided the best explanatory models for hyperinsulinaemia in subsequent remission (goodness of fit: $\chi^2=11.53$, $df=2$, $p=0.003$).

4. Discussion

4.1. Bipolar mania and hyperinsulinaemia

To the best of our knowledge, this is the first study to demonstrate the elevation of plasma insulin levels during manic episodes amongst bipolar disorder patients. There is, at this time, no universally accepted criterion for hyperinsulinaemia in the fasting state. One major finding of the present study is that hyperinsulinaemia, as defined by the criteria for both Taiwanese (Chien et al., 1999) and Western (>15 μIU/ml) (Després et al., 1996; Ferrannini and Balkau, 2002) populations, is present in approximately two thirds of bipolar patients in subsequent or early remission of acute mania, regardless of the type of mood stabilizers or antipsychotics used. Conversely, hyperinsulinaemia was not so common at the starting point of treatment for acute mania.

4.2. Medication and hyperinsulinaemia

In this study we have specifically examined whether the medication status of various psychotropic agents has any relationship with hyperinsulinaemia. Kivircik et al. (2003) found that leptin and insulin levels did not display any significant alteration across time in clozapine-treated schizophrenic patient with bodyweight gain. Furthermore, despite the increasing number of patients in subsequent remission using atypical antipsychotics and mood stabilizers, our data provide support for the notion that, rather than the direct effects of mood stabilizers or atypical antipsychotics themselves, the disproportionate increase in insulin levels may be the result of other factors.

Patients in the early phase of acute mania had comparable insulin levels which did not exceed the normal limit, irrespective of whether or not they were taking propranolol; however, our analysis indicates that the administration of this classic beta-blocker throughout the period of the manic episode may contribute to the extreme elevation of plasma insulin levels at the end-point measurement in subsequent remission. This finding provides additional evidence of concern with regard to the use of beta-blockers and the adverse metabolic effects on insulin sensitivity. Apart from the unfavorable effects on lipids or insulin sensitivity, beta-blockers can also cause weight gain and may be associated with a 0.5 kg to 3.5 kg increase in body weight after six to twelve months of treatment (Sharma et al., 2001).

Whilst a number of mechanisms have already been proposed for either lithium- or valproate-induced weight gain, considerable uncertainty remains with regard to this issue in bipolar patients (McElroy et al., 2004). Although the hyperinsulinaemic patients in this study were characterized by increasing body weight, with a mean 46-day interval between the two measurements, it is unlikely that propranolol-induced bodyweight gain has any association with elevated insulin levels. It is therefore suggested that there will be a tendency for medicated bipolar patients to gain body weight and that the use of propranolol, which exacerbates insulin resistance prior to weight gain, may play some role in hyperinsulinaemia in propranolol-treated patients. The stimulation of the β_2 adrenergic receptor results in an increase in muscle glycogenolysis and insulin release, whilst β_1-blocker can also increase insulin resistance (Podlowski et al., 1998). Our finding is therefore supported by the fact that non-selective beta-blockers tend to cause glucose intolerance (Cruickshank, 2000).

Another major finding is that hyperinsulinaemia is also present in an alarmingly high proportion of medicated bipolar patients free of any beta-blockers across the entire episode. Our results are in line with the findings that elevated plasma leptin levels have a positive relationship with increased bodyweight and BMI amongst bipolar patients (McIntyre et al., 2005), and that insulin may stimulate leptin gene expression and the secretion of its product (Lee et al., 2001). Although experimentally-induced insulin resistance diminishes the stimulatory effect of insulin on leptin secretion, insulin is nevertheless thought to be an important regulator of leptin secretion (Fruehwald-Schultes et al., 2002).

It is noted that a rapid and significant elevation in plasma insulin level is not accompanied by any proportional increments in plasma leptin, bodyweight gain or BMI. This uncoupling process indicates that circulatory insulin may deregulate leptin in manic episode, with such mechanism differing from that of normal individuals. The alteration in the immunomodulatory system (Rapaport, 1994; Tsai et al., 1999, 2001) and the metabolism of circulatory lipids (Cassidy and Carroll, 2002) may be state-dependent and may have a role to play in hyperinsulinaemia.

4.3. Smoking and hyperinsulinaemia

Since nicotine may lead to mild hyperglycemia and lower insulin sensitivity (Morgan et al., 2004), smokers are more insulin-resistant and hyperinsulinaemic (Filozof et al., 2004). Our results demonstrate the tendency for a smoking habit amongst hyperinsulinaemic bipolar patients; however, consideration of the smoking habit fails to hold when factored into the multivariate analyses for hyperinsulinaemia. One possible explanation is that the effects of smoking on insulin regulation may not depend solely on the presence of a smoking habit, but also on the total amount of nicotine, which is clearly difficult to estimate.

4.4. Methodological limitations

First, our study is limited somewhat by its failure to control for individual variations which are known to effect insulin levels (such as smoking), the permission for concomitant medication and the fact that the data were obtained for only two specific time points throughout a manic episode. Secondly, according to the DSM-IV criteria, full remission is defined as 'no significant signs or symptoms of the affective disturbance over the past two months'. No repeated measurements were taken of our bipolar patients' insulin levels during the period of full remission after a manic episode. It therefore remains to be seen whether the upward regulation of insulin is an additional state-dependent pathophysiology of bipolar mania. Finally, the side effects of insulin resistance amongst bipolar patients treated with atypical antipsychotics were not observed in this study; we therefore await further empirical confirmation before drawing any conclusion on this particular issue.

5. Conclusions

Given that the majority of bipolar patients in subsequent remission of acute mania, regardless of medication status, meet the criteria for hyperinsulinaemia, this therefore suggests that amongst bipolar disorder patients, a unique pathway exists for the regulation of insulin sensitivity during manic episodes. The elucidation of the regulatory mechanism of adipocytokines and insulin may provide some clues with regard to clarifying the pathophysiology of bipolar mania.

Despite the direction of the cause and effect relationship between hyperinsulinaemia and bodyweight gain remaining unclear, the present study does support that medicated bipolar patients, particularly those receiving propranolol, are vulnerable to hyperinsulinaemia during manic episode, which therefore suggests greater caution when co-prescribing beta-blockers.

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