See commentary by Heiskanen

Clinical Risk Factors for Weight Gain During Psychopharmacologic Treatment of Depression: Results From 2 Large German Observational Studies

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ABSTRACT

Objective: Weight gain during psychopharmacologic treatment has considerable impact on the clinical management of depression, treatment continuation, and risk for metabolic disorders. As no profound clinical risk factors have been identified so far, the aim of our analyses was to determine clinical risk factors associated with short-term weight development in 2 large observational psychopharmacologic treatment studies for major depression.

Method: Clinical variables at baseline (age, gender, depression psychopathology, anthropometry, disease history, and disease entity) were analyzed for association with percent change in body mass index (BMI; normal range, 18.5 to 25 kg/m^2) during 5 weeks of naturalistic psychopharmacologic treatment in patients who had a depressive episode as single depressive episode, in the course of recurrent unipolar depression or bipolar disorder according to *DSM-IV* criteria. 703 patients participated in the Munich Antidepressant Response Signature (MARS) project, an ongoing study since 2002, and 214 patients participated in a study conducted at the University of Muenster from 2004 to 2006 in Germany.

Results: Lower BMI, weight-increasing side effects of medication, severity of depression, and psychotic symptoms could be identified as clinical risk factors associated with elevated weight gain during the initial treatment phase of 5 weeks in both studies. Based on these results, a composite risk score for weight gain consisting of BMI ≤ 25 kg/m^2, Hamilton Depression Rating Scale (17-item) score > 20, presence of psychotic symptoms, and administration of psychopharmacologic medication with potential weight-gaining side effects was highly discriminative for mean weight gain ($F_{4,909}$ = 26.77, P = 5.14E-21) during short-term psychopharmacologic treatment.

Conclusions: On the basis of our results, depressed patients with low to normal BMI, severe depression, or psychotic symptoms should be considered at higher risk for weight gain during acute antidepressant treatment. We introduce a new risk score that might be considered in psychopharmacologic decisions for the prevention of weight gain and resulting metabolic disorders.

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Weight gain during psychopharmacologic therapy for major depression is a crucial factor for acceptability and continuation of treatment.[1–4] Besides having a major effect on stability of treatment and relapse prevention, weight gain increases the probability for metabolic and vascular disorders (eg, obesity, hypertension, dyslipidemia, type 2 diabetes and cardiovascular disease).[5–7] Despite the fact that weight loss is recognized as a frequent symptom during depressive episodes,[8,9] a strong relationship between major depression and obesity has been described,[10] suggesting that regaining weight during recovery from depression in addition to weight- and appetite-increasing side effects of several psychopharmacologic substances[2,3] may override the acute weight loss effect during depressive episodes in long-term disease course.

Distinct and marked differences in the effects of specific psychopharmacologic drugs on appetite and weight have been described extensively.[3,11] While several tricyclic antidepressants, mirtazapine, lithium, valproate, and a number of second-generation antipsychotics frequently lead to a considerable increase in weight, other psychopharmacologic agents, for example bupropion or topiramate, have been described to commonly decrease appetite and weight during administration or probably have no potential to exert strong weight- or appetite-changing effects.[2,3,11]

In addition, some selective serotonin reuptake inhibitors (SSRIs), eg, citalopram, escitalopram, or paroxetine, and serotonin and norepinephrine reuptake inhibitors (SNRIs), eg, duloxetine, have been shown to possibly exert different effects on weight development with weight decrease during acute treatment and weight increase during long-term treatment.[12]

Apart from these obvious drug-specific effects, high interindividual differences suggest the presence of highly relevant drug-independent influences on treatment accompanying weight change.[9,13–17]

Although weight gain during treatment is a daily recognizable and frequently occurring issue in everyday clinical practice, only a few and mostly small studies have brought forth evidence on risk factors or predictors of weight development during treatment. Among these studies, Fernstrom and Kupfer[15] reported no association of weight change with age, gender, depression severity, obesity, or weight loss during depression in 73 depressed patients. Recently, Heiskanen et al[18] described severity of depression psychopathology and adverse experiences as predictors for long-term weight gain over 6 years in 121 depressed outpatients. Regarding baseline weight as a predictor

Clinical Points

- Lower body mass index, weight-increasing side effects of medication, higher severity of depression, and psychotic symptoms were identified as clinical risk factors for weight gain during acute psychopharmacologic treatment of patients with depression in 2 large observational studies.
- Based on these findings, a composite clinical risk score was developed that might be considered as additional information for treatment decisions, individualized disease management, and risk prevention for metabolic disorders in the treatment of depression.

for weight change during psychopharmacologic treatment, depressed patients with obesity on average lost weight during treatment in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study (n = 630).[16] This finding is concordant with our previous report of less weight gain in overweight and obese patients with major depression during treatment.[19] In other studies, this association of baseline weight with treatment-emerging weight changes could not be detected.[9,15,17]

In consideration of treatment-associated weight gain as an important clinical issue, robust identification of risk factors is clearly needed to provide better information or criteria for individualized psychopharmacologic decisions and monitoring strategies. Therefore, the aim of our analyses was to identify clinical factors associated with weight change during acute psychopharmacologic treatment during 5 weeks in 2 large observational studies in major depression, the Munich Antidepressant Response Signature (MARS) project[20] and a study conducted at the University of Muenster in Germany.[21]

METHOD

MARS Sample

The MARS project was initiated in 2002 and is an ongoing naturalistic treatment study in white inpatients suffering from major depression and admitted to the Max Planck Institute of Psychiatry and collaborating study sites; the project has been previously described in detail.[20] The study was approved by the local Ethics Committee of the Ludwig Maximilian University, Munich, Germany, and written informed consent was obtained from all participants after detailed study information was provided. Patients had a current major depressive episode (MDE) as single MDE, in the course of recurrent unipolar depression or bipolar disorder. *DSM-IV* criteria[22] were applied for diagnoses by trained psychiatrists. Depressive syndromes based on neurologic or any other medical conditions, actual presence of manic/hypomanic symptoms, lifetime diagnoses of alcohol dependence or drug abuse, and severe medical conditions were exclusion criteria.

Clinical information of disease history (age at disease onset, disease duration, and bipolar and/or recurrent disease course) was collected and Hamilton Depression Rating Scales (HDRS, 21-item)[23] were obtained at admission. Height and weight measurements were conducted at admission using calibrated height meters and scales. Weight was measured in the morning under fasting conditions in light clothing. Patients were weighed in weekly intervals. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2) (BMI normal range, 18.5 to 25 kg/m^2).

Muenster Sample

White inpatients with a current MDE as a first episode or in the course of recurrent unipolar depression or bipolar disorder were recruited at the Department of Psychiatry, University of Muenster, Muenster, Germany, between 2004 and 2006. Study details have been described elsewhere.[21] The study was approved by the ethics committee of the University of Muenster, Germany. After complete information was provided to the subjects, written informed consent was obtained. Diagnoses were obtained using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I).[24] Patients with substance abuse disorders, mental retardation, neurologic, or neurodegenerative disorders, as well as pregnant patients, were excluded. Depression psychopathology was assessed using the HDRS (21-item). Detailed clinical information of disease history was obtained comparably to the MARS sample. Height and weight measurements were conducted using calibrated height meters and scales. Additionally, patients were weighed in weekly intervals.

Patients' Selection and Clinical Variables

From both studies, only subjects with a complete record of clinical data, disease history data, HDRS ratings, weight measurements, and detailed weekly information on psychopharmacologic treatment were used for analysis. Further inclusion criteria were HDRS (17-item) scores ≥ 8 and BMI > 17 kg/m^2 or < 50 kg/m^2 at baseline. Patients with inconsistent weight measurements during treatment were excluded. After applying these criteria, 703 subjects from the MARS project and 214 from the Muenster study entered the analyses.

Appetite loss and psychotic symptoms at baseline were defined using the respective items from HDRS (21-item) ratings at admission. As psychotic symptoms influence the treatment of depression and selection of psychopharmacologic substances, the HDRS (17-item) was used to assess depression severity for better differentiation of these psychopathological features in the analyses.

Percent change in BMI over 5 weeks of psychopharmacologic treatment was applied as the main outcome parameter for weight change in all analyses.

To analyze medication-independent effects and to control for known potential weight-changing side effects of the different psychopharmacologic substances, 2 variables representing the relative time of administration of medication with potential weight-increasing side effects (med-gain) and relative time under medication with potential weight reducing side effects (med-loss) were calculated. In this context, all psychopharmacologic substances were allocated

Table 1. Baseline Characteristics of the MARS and Muenster Samples

	MARS Sample			Muenster Sample		
Characteristic	N	Mean	SD	N	Mean	SD
Age, y	703	47.88	13.91	214	50.35	14.47
BMI at admission (kg/m^2)		25.81	4.78		25.79	5.07
HDRS (17-item) score at admission		24.21	6.11		21.92	7.16
Appetite loss (HDRS item 12)		0.78	0.66		0.68	0.62
Age at disease onset, y		36.13	15.05		41.23	15.22
Disease duration, y		11.74	12.24		9.56	9.54
	N	%		N	%	
Gender (females)	355	50.50		122	57.01	
Bipolar disorder	91	12.94		18	8.41	
Psychotic symptoms at admission	96	13.66		25	11.68	
Single depressive episode	172	24.47		69	32.25	
	N	Mean	SD	N	Mean	SD
Weight change (5 wk), kg	703	0.60	3.04	214	1.64	3.91
BMI change (5 wk) (kg/m^2)		0.21	1.01		0.55	1.33
BMI change percent (5 wk), %		1.03	4.06		2.44	5.51
BMI change per week (5 wk) (kg/m^2)		0.041	0.20		0.11	0.27
Relative duration of potential weight-increasing medication (med-gain)		0.72	0.39		0.78	0.32
Relative duration of potential weight-decreasing medication (med-loss)		0.62	0.42		0.61	0.34

Abbreviations: BMI = body mass index, HDRS = Hamilton Depression Rating Scale, MARS = Munich Antidepressant Response Signature project.

Table 2. BMI Change in Percent During 5 Weeks of Treatment in Different Medication Groups (Antidepressant Monotherapy, Comedication Antipsychotics, Mood Stabilizers, Benzodiazepines)

			BMI Change in % (5 Wk)			
MARS Sample	N	%	Mean	SD	*F*	*P*
Antidepressant monotherapy[a,b]	253	35.99			16.66[c]	6.91E-10
SSRIs	81	11.52	−0.17	2.84		
SNRIs	71	10.10	−1.07	3.85		
TCAs	39	5.55	1.02	3.96		
Mirtazapine	62	8.82	2.85	3.15		
Comedication antipsychotics	202	28.73	1.78	4.45		
No comedication antipsychotics	501	71.27	0.72	3.85	10.84[d]	1.00E-03
Comedication mood stabilizers	167	23.76	0.68	4.04		
No comedication mood stabilizers	536	76.24	1.13	4.06	1.51[d]	.22
Comedication benzodiazepines	232	33.00	1.40	4.16		
No comedication benzodiazepines	471	67.00	0.84	4.00	3.56[d]	.059

[a]No antidepressant combination treatment, no comedication with antipsychotics.
[b]Pairwise comparisons were significant: SSRI vs mirtazapine: $P = 1.35E-07$; TCA vs mirtazapine: $P = .0070$; TCA vs SNRI: $P = .0029$; SNRI vs mirtazapine: $P = 1.96E-10$), except for SSRI vs SNRI group ($P = .18$) and a trend for SSRI vs TCA ($P = .055$).
[c]$F_{3,247}$.
[d]$F_{1,699}$.
Abbreviations: BMI = body mass index, MARS = Munich Antidepressant Response Signature project, SNRI = serotonin and norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants.

following the review and suggestions by Zimmermann et al[3] for short-term treatment effects.

Detailed information on baseline characteristics and the clinical variables for both samples are provided in Table 1. The comparison of both samples revealed differences among the following variables: Mean age, age at disease onset, and proportion of patients with single depressive episode were lower in the MARS sample; disease duration and mean HDRS scores were higher in the MARS sample. Mean weight gain and proportional time of medication with potential weight increasing side effects (med-gain) were higher in the Muenster sample.

Statistical Analysis

Percent BMI changes in different medication groups were analyzed using the general linear model and partial correlation with age and gender as covariates.

Analyses of clinical predictors (age, gender, BMI, HDRS [17-item], appetite loss, psychotic symptoms at baseline, age at disease onset, disease duration, unipolar depression/bipolar disorder, single/recurrent depressive episodes, med-gain, and med-loss) for percent BMI change were performed by applying partial correlation for each variable in both samples. Then, the variables from the analyses that showed a significant association with percent BMI change in both samples were analyzed in the combined sample (MARS + Muenster) with multivariate linear regression to discriminate independent effects of these variables. Finally, clinical variables associated with BMI change in both studies were used for the composition of the clinical risk score. Analyses of risk score with percent BMI change were performed with the general linear model using age and gender as covariates. Sample was added as covariate for analysis in the combined sample.

IBM SPSS Version 20 was used for all statistical analyses.

RESULTS

MARS Sample

Patients in the MARS sample (n = 703) displayed a mean weight gain of + 0.60 kg (BMI change: + 0.21 kg/m^2, BMI change in percent: + 1.03%) during 5 weeks of treatment. Weight gain was observed in 56.33% of patients.

Medication. On average, patients received medication with potential weight-increasing side effects (med-gain) during 72% (± 39% [SD]) of the 5-week observation period and medication with potential weight-decreasing side effects (med-loss) during 62% (± 42% [SD]) of the 5-week observation period (Table 1).

A substantial difference among different antidepressant classes on acute weight development could be detected when comparing patients receiving antidepressant monotherapy (n = 253, $P = 6.91E-10$; Table 2). Patients receiving SSRI or SNRI treatment showed a decrease in mean BMI, whereas

Table 3. Correlation of Clinical Variables and Percent Change of BMI During 5 Weeks of Treatment[a]

	MARS Sample (N = 703)		Muenster Sample (N = 214)	
Clinical Variable	Correlation (*r*)	*P*	Correlation (*r*)	*P*
Med-gain[b]	0.259	3.01E-12	0.147	.016
Med-loss	−0.119	1.65E-03	−0.073	.14
Age	−0.062	.10	0.032	.32
Gender	0.017	.65	0.004	.48
BMI[b]	−0.305	1.32E-16	−0.253	9.02E-05
HDRS (17-item)[b]	0.166	1.03E-05	0.138	.022
HDRS appetite loss	0.140	1.94E-04	0.063	.18
Psychotic symptoms[c]	0.079	.036	0.112	.051
Age at disease onset	−0.008	.83	0.057	.20
Disease duration	−0.060	.11	−0.049	.24
Unipolar/bipolar	−0.010	.80	−0.061	.19
Recurrent depression	−0.021	.58	−0.063	.18

[a]*P* values: MARS sample (2-tailed), Muenster sample (1-tailed).
[b]Significant association with BMI change in both samples.
[c]Significant association with BMI change in the MARS sample; suggestive trend in the Muenster sample.
Abbreviations: BMI = body mass index, HDRS = Hamilton Depression Rating Scale, MARS = Munich Antidepressant Response Signature project, med-gain = proportional duration of potential weight increasing medication, med-loss = proportional duration of potential weight decreasing medication.

patients treated with tricyclic antidepressants (TCAs) or mirtazapine on average gained weight. Pairwise medication group comparisons displayed a significant difference (Table 2) in mean percent BMI change over 5 weeks (SSRI vs mirtazapine: $P = 1.35E-07$; TCA vs mirtazapine: $P = .0070$; TCA vs SNRI: $P = .0029$; SNRI vs mirtazapine: $P = 1.96E-10$), except for SSRI vs SNRI group ($P = .18$) and a trend for SSRI vs TCA ($P = .055$).

Further comparisons of groups receiving concomitant nonantidepressant medication revealed a significant association of antipsychotic comedication with weight gain ($P = .0010$), while coadministration of mood-stabilizers or benzodiazepines showed no significant effect on weight change (Table 2).

A regression analysis using the different medication variables described above revealed med-gain and med-loss as the most relevant variables for a medication effect on BMI change during 5 weeks (med-gain: $\beta = 0.225$, $P = 1.52E-08$; med-loss: $\beta = -0.079$, $P = .036$; and antipsychotic comedication: $\beta = 0.061$, $P = .12$). Hence, these variables (med-gain and med-loss) were used in all further analyses.

Clinical variables. Lower BMI ($P = 1.32E-16$), higher depression severity ($P = 1.03E-05$), appetite loss during depressive episode ($P = 1.94E-04$), psychotic symptoms ($P = .036$), and proportional time receiving medication with potential weight-increasing side effects (med-gain, $P = 3.01E-12$) were significantly correlated with increase in percent BMI during 5 weeks of psychopharmacologic treatment (Table 3). Time of administration of medication with potential weight-reducing side effects (med-loss, $P = 1.65E-03$) was inversely correlated with weight gain (Table 3).

When controlling for age, gender, med-gain, and med-loss, all correlations remained significant, suggesting medication independent effects on weight change of these clinical variables.

Table 4. Risk Score for Weight Gain[a]

Risk Score	0			1		
BMI	> 25			≤ 25		
Medication (weight-gain)	No			Yes		
HDRS (17-item)	≤ 20			> 20		
Psychotic symptoms	No			Yes		
	MARS Sample (N = 703)			Muenster Sample (N = 214)		
Risk-Score groups	N	Mean	SD	N	Mean	SD
0	25	−2.78	3.31	3	−0.79	4.93
1	128	−0.22	3.71	60	0.73	4.76
2	298	0.70	3.73	84	1.75	4.75
3	213	2.00	4.06	55	4.94	6.31
4	39	4.72	3.97	12	5.22	6.00
	$F_{4,696} = 22.38$; $P = 2.09E-17$			$F_{4,207} = 6.30$; $P = 8.34E-05$		
Cumulative Risk-Score groups						
0–2	451	0.25	3.79	147	1.28	4.76
3–4	252	2.42	4.16	67	4.99	6.21
	$F_{1,699} = 48.18$; $P = 8.85E-12$			$F_{1,210} = 23.14$; $P = 2.87E-06$		

[a]Risk-score groups (0–4) for weight gain (percent change in BMI during 5 weeks of treatment) as sum of 4 clinical variables: (1) baseline BMI (0: BMI > 25, 1: BMI ≤ 25), (2) administration of medication with potential weight-inducing side effect (0: no, 1: yes), (3) depression severity (0: 17-item HDRS score ≤ 20, 1: 17-item HDRS score > 20), (4) psychotic symptoms (0: no, 1: yes).

Interestingly, a trend was present that med-gain was lower in patients with a higher BMI at baseline, though this effect was not statistically significant when controlled for age, gender, and HDRS (17-item) score at admission. Additionally, comedication with antipsychotics was not associated with baseline BMI. The latter results suggest that the strong effect of baseline BMI on weight change is not driven by great differences in the selection of psychopharmacologic substances among normal and overweight patients. In this context, we were able to substantiate our finding that patients who are overweight and obese (BMI > 25) show significantly less mean weight gain[19] compared to patients with BMI ≤ 25 in this larger sample (percent BMI change: BMI ≤ 25 [n = 340] + 2.11%; BMI > 25 [n = 363] +0.0076%; $F_{1,699} = 48.24$, $P = 8.63E-12$).

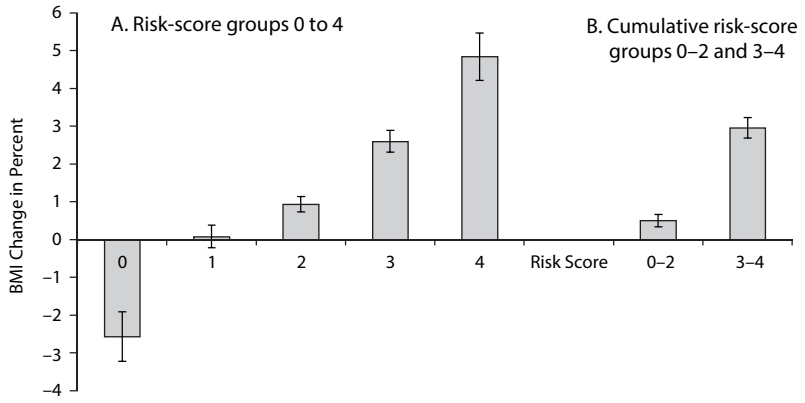
Muenster Sample

As the study protocol is very similar to the MARS study, the Muenster sample was used to replicate the findings from the MARS study. Patients in this sample (n = 214) showed a mean weight gain of + 1.64 kg (BMI change: + 0.55 kg/m^2, BMI change in percent: + 2.44%) during 5 weeks of treatment. Weight gain was observed in 68.22% of patients.

Medication. Due to the lower sample size, subgroups were not of adequate quantity for differential analysis of single medication classes.

Clinical variables. Correlations of lower BMI ($P = 9.02E-05$), higher depression severity ($P = .022$), time receiving medication with potential weight-increasing side effects (med-gain, $P = .016$), and presence of psychotic symptoms could be validated in the Muenster sample, although the variable psychotic symptoms narrowly missed the level of statistical significance ($P = .051$). The association of BMI

Figure 1. BMI Change in Percent[a] (5 Weeks) by Risk Score[b] for Weight Gain (combined sample)[c]



[a]Means and standard errors of the mean are presented.
[b]Risk-score groups (0–4) for weight gain (percent change in BMI during 5 weeks of treatment) as sum of 4 clinical variables: (1) baseline BMI (0: BMI > 25, 1: BMI ≤ 25), (2) administration of medication with potential weight-inducing side effect (0: no, 1: yes), (3) depression severity (0: 17-item HDRS score ≤ 20, 1: 17-item HDRS score > 20), (4) psychotic symptoms (0: no, 1: yes).
[c]Combined sample (MARS + Muenster samples [n = 917]).
Abbreviations: BMI = body mass index, HDRS = Hamilton Depression Rating Scale, MARS = Munich Antidepressant Response Signature project.

change with med-loss or appetite loss during depressive episode could not be replicated in the Muenster study (Table 3).

Combined Sample

Several of the investigated predictors for percent BMI change are intercorrelated in the combined sample. For instance, age is considerably associated with age at disease onset ($r = 0.67$, $P < .001$) and actual disease duration ($r = 0.31$, $P < .001$); age at disease onset is associated with actual disease duration (inverse association, $r = -0.48$, $P < .001$) and recurrent depression (inverse association, $r = -0.24$, $P < .001$); and the total HDRS (17-item) score is associated with the HDRS item appetite loss ($r = 0.44$, $P < .001$) and with the presence of psychotic symptoms ($r = 0.27$, $P < .001$). BMI is inversely correlated with the HDRS item appetite loss ($r = -0.21$, $P < .001$).

For all variables showing an association with percent BMI change in the MARS and Muenster samples (med-gain, BMI, HRDS score, and psychotic symptoms), significant correlations could also be detected in the combined sample. To discriminate independent effects of these variables on acute weight change, we performed a multiple regression analysis including these variables. The results revealed significant independent effects of baseline BMI ($\beta = -0.269$, $P = 1.74E\text{-}17$), med-gain ($\beta = 0.220$, $P = 2.11E\text{-}12$), and depression severity ($\beta = 0.069$, $P = .034$) on BMI change during 5 weeks of treatment in descending order. Additionally, a trend could be detected for psychotic symptoms at baseline ($\beta = 0.050$, $P = .11$).

Risk Score for Weight Gain

As the aim of our study was to provide clinicians with useful factors for estimation of weight gain in patients under a planned psychopharmacologic treatment, we attempted to create a composite risk score for weight gain based on the results of our analyses. Therefore, clinical variables associated with BMI in both studies were used to create an easily applicable risk score. Even though the association of weight gain with presence of psychotic symptoms was less pronounced in the Muenster sample and in the regression analysis, we included psychotic symptoms as a variable in the composition of the risk score due to the relevance of this psychopathological feature in the treatment and selection of psychopharmacologic medication.

The risk score (0–4) was composed as the sum of 4 clinical variables: BMI (BMI > 25: 0, BMI ≤ 25: 1), use of medication with potential weight-increasing side effect (no: 0, yes: 1), depression severity (HDRS [17-item] ≤ 20: 0, HDRS [17-item] > 20: 1), and presence of psychotic symptoms (no: 0, yes: 1) (Table 4).

Applying the risk score in the MARS study, a significant and highly discriminative effect on mean percent change of BMI was observed ($P = 2.09E\text{-}17$; Table 4). Pairwise comparisons among all 5 risk-score groups (0–4) were significant. In particular, risk-score groups 3 and 4 showed a clinically relevant gain in mean percent BMI over 5 weeks. Therefore, we additionally performed an analysis comparing patients in cumulative risk-score groups 0–2 with patients in cumulative risk-score groups 3–4 ($P = 8.85E\text{-}12$; Table 4).

The risk score analysis in the Muenster sample corroborated the finding in the MARS study (single risk-score groups: $P = 8.34E\text{-}05$, cumulative risk-score groups: $P = 2.87E\text{-}06$; Table 4). Pairwise comparisons were significant between risk-score groups 1 and 3, 1 and 4, 2 and 3, and 2 and 4.

Furthermore, percent BMI change during 5 weeks in the combined sample (n = 917) among risk-score groups

($F_{4,909} = 26.77$, $P = 5.14E-21$) and cumulative risk-score groups (0–2 and 3–4; ($F_{1,912} = 71.70$, $P = 9.94E-17$) was significantly different and is illustrated in Figure 1. In this combined sample analysis, all pairwise comparisons were significant, pointing toward a highly discriminative effect of the risk-score groups with regard to mean percent BMI change in the combined sample.

DISCUSSION

In 2 large naturalistic studies of psychopharmacologic treatment in depression (MARS project and Muenster study), BMI, weight changing side effects of medication, severity of depression, and presence of psychotic symptoms could be significantly linked to acute initial weight development during 5 weeks of treatment. BMI and a potential weight-increasing side effect of medication were the most relevant factors for weight gain in both samples. Furthermore, higher depression severity and the presence of psychotic symptoms were significantly correlated with acute weight gain.

As weight gain during pharmacologic treatment of depression is a clinically relevant and often crucial issue for treatment stability, compliance, disease course, and the development of secondary metabolic disorders,[1–3,5,11] we attempted to create a potentially applicable clinical risk score for acute treatment-associated weight gain in depressed patients based on our results. This composite risk score is composed as a sum score from 0 to 4 using the following criteria: (1) BMI ≤ 25, (2) administration of medication with potential weight-increasing effects, (3) HDRS (17-item) score > 20, and (4) presence of psychotic symptoms.

The association of higher BMI with lower weight gain or even weight loss during treatment is supported by findings in the Genome-Based Therapeutic Drugs for Depression (GENDEP) study reported by Uher and colleagues.[16] As reported above, the patient group with BMI > 25 showed only slight mean weight changes in the MARS study, even though no significant differences in selection of medication could be detected. Based on these results, a lower risk for weight gain in overweight and obese patients could potentially be considered in clinical treatment decisions.

Other previous studies were not able to detect an influence of baseline body weight on treatment-associated weight changes.[9,15,17] Contradictory findings for weight gain during the psychopharmacologic treatment of schizophrenia have been reported,[3] although several studies in this context also reported lower weight to be associated with later treatment-induced increase in weight.[25,26]

The finding of higher depression severity being associated with weight gain in both samples has also been reported recently by Heiskanen et al[18] in a long-term observation over 6 years. Other studies did not detect this relationship.[15]

To critically evaluate our findings, we want to address the limitations of our studies and analyses:

As we analyzed retrospective data, precise or definite assumptions or decision criteria cannot be drawn from the results at this point. To substantiate and specify these findings, prospective studies and further replications are needed. The studies used for this analysis followed a naturalistic observational design with treatment diversity. However, previously reported weight-changing effects of different classes of antidepressants[2,3,11] could be clearly demonstrated when analyzing subgroups of patients receiving antidepressant monotherapy.

As the studies were conducted in inpatients during acute treatment, conclusions about risk factors for weight development during longer treatment periods cannot be provided. Although sustained weight development is more relevant for long-term metabolic and vascular risk, several reports have highlighted that clinically relevant weight changes and alterations in glucose or lipid metabolism may occur even during short-term psychopharmacologic treatment.[14,27,28] Furthermore, initial weight gain has been shown to predict long-term weight development during treatment.[29] For a subgroup of the MARS study with prolonged hospitalization (> 10 weeks; n = 357), we were able to evaluate a high correlation of BMI in week 5 with BMI at discharge ($r = 0.967$, $P = 2.5E-211$) and BMI change during 5 weeks with BMI change from admission to discharge ($r = 0.708$, $P = 4.0E-55$) or from week 5 to discharge ($r = 0.208$, $P = 1.1E-4$). Nevertheless, reliable assumptions on long-term weight development cannot be drawn from our results, and we were unable to consider or assume the differential acute- and maintenance-treatment effect of some SSRIs and SNRIs on weight change,[12] as our findings are based solely on short-term observations.

As we have examined only acute treatment effects, weight gain in this treatment period could be partly explained by a recovery from appetite and weight loss before hospitalization. Otherwise, appetite loss was not significantly associated with acute weight change in the Muenster study and was highly correlated with total HDRS score.

The normality assumption, which is one of the prerequisites of linear regression analysis, was violated for some of the predictor variables including med-gain, med-loss, BMI, age at disease onset, and disease duration (Kolmogorov-Smirnov tests, $P < .05$, data not shown). However, the large sample size and the availability of a replication sample should limit the risk of false positive findings due to outlier values. Indeed, when applying the nonparametric Kendall Tau-b rank correlation test instead of linear regression, the same association pattern for the set of weight-change predictors could be shown for both samples, moreover, the association with psychotic symptoms turned from a suggestive effect ($P = .051$) to a significant effect ($P = .029$) in the Muenster sample (data not shown).

When reconsidering our results detached from the strong focus on weight gain, the findings could be relevant for patients with a high BMI at baseline, as these patients are believed to be at particular risk for further weight gain. Due to this perception, potentially effective psychopharmacologic treatment options with weight gain as a side effect might be withheld from patients with high BMI.

Even though an accurate prediction of acute individual weight development cannot be derived from these results,

potential risk estimation for weight gain in patients seems possible by applying the clinical risk factors and the proposed composite risk score resulting from these 2 large treatment studies. Besides these possible clinical predictors, the different potential among drugs on weight change, dosage, length of treatment, or clinical response should be considered for the estimation of weight course in depressed patients.[3,11]

In considering the attempt for risk differentiation by composing a risk score, the clinical variables from our studies seem to show a cumulative effect on weight gain (Table 4 and Figure 1). Based on our findings, we would recommend critically considering the administration of potential weight-inducing psychopharmacologic substances to depressed patients presenting with risk factors such as severe depression, low BMI, or psychotic symptoms.

Apart from determining clinical risk factors of weight gain during psychopharmacologic treatment, further research in this crucial area should focus on biological or genetic markers, as reliable prediction of psychopharmacologic treatment–associated weight gain is clearly needed to improve individualized treatment strategies and clinical disease management and to prevent metabolic and vascular disorders in major depression and other mental disorders.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), lithium (Lithobid and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), topiramate (Topamax and others).

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