sponsive to this treatment. Unfortunately, a novel dramatic increase in weight was observed, with an additional 8-kg gain over 1 month. Discontinuation of escitalopram and replacement by topiramate was followed by weight stabilization.

A phasic craving for carbohydrate has been described with citalopram (4) and paroxetine (4, 5). As during escitalopram treatment, a decrease in weight gain followed transient discontinuation of quetiapine, so we may attribute the weight gain to the specific association rather than understand it as an unusual weight gain with escitalopram. As far as we know, a weight gain resulting from an association of quetiapine and escitalopram has not been reported.

Susceptibility to weight gain was obvious for this patient, and an overweight family trend could explain part of her predisposition. However, the weight gain induced by quetiapine was absent before the introduction of escitalopram. Therefore, the association of quetiapine and escitalopram appears to potentiate dramatically the neuroleptic-induced weight gain and should lead to further investigation. Antipsychotic-induced weight gain could be mediated by different factors, including important ones that are independent from the antipsychotic treatment itself.

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Transcranial Magnetic Stimulation for Refractory Depression

TO THE EDITOR: Several studies have shown that repetitive transcranial magnetic stimulation is effective in the treatment of acute depressive symptoms (1). However, the maintenance effect of this technique has not yet been assessed. In this study, we sought to investigate the capability of repetitive transcranial magnetic stimulation, when administered regularly over a period of 3 months after an acute phase, in maintaining its efficacy with refractory treated depressed patients.

Eleven refractory depressed patients were included in this open study: six women and five men with a mean age of 47.18 years (SD=12.83) and a duration of illness of 9.03 years (SD=7.5). All participants gave their informed consent after receiving a detailed explanation of the study. Patients were recruited if they did not respond to at least two different antidepressants. Treatment parameters were as follows: stimulation over the left dorsolateral prefrontal cortex, 10 Hz, 80% of the motor threshold, 26 trains, 1600 pulses. They received one daily session over 2 weeks then three weekly sessions for 2 weeks. At the end of the first month, the patients received one weekly session over 1 month and then one session each fortnight.

The patients were assessed with the Hamilton Depression Rating Scale at baseline, after 1 month, and then after 4 months. Mean score on the Hamilton depression scale at baseline was 24.1 (SD=3.7).

Statistical analysis showed that mean Hamilton depression scale scores had decreased significantly by the end of the first month (mean=10.27, SD=3.87) (analysis of variance [ANOVA] for repeated measures followed by the Tukey-Kramer multiple comparison test, df=2, 30, p=0.003). At the end of the trial, the scores were maintained, and no statistical difference was found between the week 4 scores and the final scores (mean=10.36, SD=5.1) (ANOVA for repeated measures followed by the Tukey-Kramer multiple comparison test, df=2, 30, p=0.91). Moreover, eight patients were responders (with more than 50% reduction in Hamilton depression scale scores). Repetitive transcranial magnetic stimulation was well tolerated, and no side effects were noted.

All patients had improved after 4 weeks of treatment. This effect was maintained during the next 3 months. Even though our study was an open trial, the significance of these results are interesting regarding some difficulties found in the treatment of refractory depression.

The most robust findings were, first, the acute efficacy of repetitive transcranial magnetic stimulation with refractory depressed patients and, second, its maintenance effect over a period of 4 months. Nevertheless, only a few open studies are available concerning the maintenance effect of repetitive transcranial magnetic stimulation after the end of the cure (2 to 20 weeks) (2), and it deserves further double-blind studies.

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Evidence of Depressive Mixed States

TO THE EDITOR: The article on agitated depression in bipolar depression by Mario Maj, M.D., Ph.D., et al. (1) is a considerable contribution to our understanding of the nature and clinical implications of depressive mixed states in bipolar I disorder. The authors reported that manic symptoms during a depressive episode are considerably overlapping with agitated depression in bipolar I depressives. The data also implied that bipolar I depressives with and without depressive

mixed states may require differential acute therapeutic strategies and may present differential long-term outcomes.

However, there are two limitations in the data presentations. First, the results on anxiety symptoms were not reported. Agitation during a depressive episode has sometimes been related to extremely severe anxiety, while many studies have reported that subjects with bipolar I depression less frequently show anxiety symptoms than unipolar depressives (2). It is important to know how three symptom clusters—agitation, mania, and anxiety symptoms—are related in bipolar I depressives. The relationship among the three symptom clusters may have led to a definitive answer to the longstanding question of whether agitation during a bipolar I depressive episode is related more to severe anxiety or to admixed manic symptoms, as the classic authors recognized it. Second, the lack of data on patients with unipolar and bipolar II depression may lead to readers' failure to take a general view of manic symptoms during a depressive episode since two separate research groups already started to observe manic symptoms during a depressive episode in both unipolar and bipolar depressives. Benazzi (3) reported that manic symptoms during a depressive episode were more frequent in outpatients with bipolar II disorder than unipolar depressive disorder. However, more than 10% of unipolar depressives had considerable manic symptoms. Our Munich study (4, 5), which included subjects with bipolar I depression as well, provided similar results. The Munich study also factor-analyzed a broad range of depressive and manic symptoms, including anxiety symptoms. In the analysis, the agitated manic factor, which is composed of psychomotor/thought excitement and irritability, was extracted separately from the anxiety factor in 95 subjects with bipolar disorder and 863 subjects with unipolar depression combined, a finding suggesting that agitation and manic symptoms compose one salient syndrome independent of anxiety in depressive disorders. Consistent with the results of Dr. Maj et al., euphoria and grandiosity did not load on our agitated manic factor.

As the authors acknowledged, more appropriate treatment strategies might be developed in the future when one takes depressive mixed states into account. The therapeutic implications of depressive mixed states would be more important in patients who have not ever experienced a hypomanic or manic episode. Patients with depressive mixed states are likely to be diagnosed as suffering from unipolar depression, according to DSM-IV. However, there is some evidence suggesting that these patients have a bipolar nature in terms of age at first onset of mood disorder and family history of bipolar disorder (5, 6). Evidence of depressive mixed states, emerging in unipolar as well as bipolar I depressives, seems to necessitate a reconsideration of the DSM-IV boundary between unipolar and bipolar disorders.

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Dr. Maj and Colleagues Reply

TO THE EDITOR: We are grateful to Dr. Sato et al. for their letter, which confirms the current revival of interest in agitated bipolar depression as a possible mixed state. Dr. Sato et al. state that in our article we did not report on anxiety symptoms in our bipolar I patients with an index episode of agitated depression. This is not correct. In Table 3 of our article, we did report the mean score on the item "inner tension" of the Comprehensive Psychopathological Rating Scale (defined in the scale as "mental tension mounting to panic, dread, and anguish"). This score was significantly higher in patients with agitated depression (mean=1.40, SD=0.49) than in those with nonagitated depression (mean=0.95, SD=0.56) ($F=21.5$, $df=1, 120$, $p<0.001$) and in those with mania (mean=0.46, SD=0.50) ($F=107.6$, $df=1, 120$, $p<0.0001$). Of the eight patients with agitated depression who showed both three symptoms of factor 2 and all of the symptoms of factor 5 of Cassidy et al. (1) for mania, six (75%) had a score of at least 1 on the "inner tension" item. In line with these findings, Koukopoulos et al. (2) used the expression "anxious-excited depression" to identify the mixed depressive state and listed "intense inner tension" as one of the symptoms characterizing the condition, whereas Akiskal and Mallya (3) mentioned "refractory anxiety" among the symptoms of mixed depression. Perhaps the current characterization of the "new" psychopathology of mania (reflected in our current assessment instruments) is not sophisticated enough to allow a clear demarcation between "anxiety" and "nonclassic manic" symptoms.

We agree with Dr. Sato et al. that the issue of agitated depression as a possible mixed state is also relevant to bipolar II and unipolar depression, and we are currently studying two cohorts of bipolar II and unipolar patients with an index episode of agitated depression, along with appropriate comparison groups.

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