Olanzapine in Male and Female Adolescent Patients With Schizophrenia and Related Disorders

Minor Sex Differences in Outcomes

To the Editors:

Schizophrenia is often first diagnosed in early adulthood, but in about one third of the cases, the disorder already developed during adolescence. 
Adolescent-onset schizophrenia is considered to be associated with a particularly poor prognosis, which underscores the need for a safe and effective treatment. In addition, sex differences in schizophrenia have been of particular interest. Although lifetime risk and prevalence seem comparable for male and female patients, differences in various aspects of the disease have been reported, for example, age of onset, premorbid state, pathophysiology, symptoms, course, coping and social skills, cognitive performance, structural brain abnormalities, treatment response and outcome. 
Many of the variables indicate that females are more likely to manifest less severe forms of the illness. 
Children and adolescents are at particularly high risk for treatment-emergent extrapyramidal symptoms during treatment with typical antipsychotics; therefore, atypical antipsychotics are often considered the treatment of choice. 
But there are few regulatory approvals for this population, for example, the US Food and Drug Administration recently approved risperidone and aripiprazole for schizophrenia (ages 13–17 years) and manic/mixed episodes in bipolar I disorder (ages 10–17 years), and there is still a lack of large prospective long-term studies.

Olanzapine has been approved for the treatment of adults with schizophrenia and bipolar disorder. 
Together with risperidone, olanzapine is currently the most commonly used atypical antipsychotic in pediatric patients (aged 18 years or younger), and therefore merits further evaluation of its effectiveness and tolerability. It is currently not regulatory-approved for the treatment of children and adolescents. Various open-label studies have suggested that olanzapine may be effective in this population, but these studies showed a number of limitations. 

A first large prospective open-label multicenter trial with an atypical antipsychotic compound (olanzapine) in this age group (12–21 years; N = 96) was performed in Germany. Then, 2 placebo-controlled trials with olanzapine in adolescents (schizophrenia, bipolar mania) have been published. 

There is only very limited information on sex differences in adolescent patients with schizophrenia. Thus, the objective of secondary analyses was to compare male and female adolescent patients from the German study with respect to selected BL (BL) characteristics plus effectiveness and tolerability parameters in an exploratory approach.

This was a 24-week, open-label, prospective trial of olanzapine in male and female adolescent patients with Diagnostic and Statistical Manual of Mental Disorders-IV schizophrenia (methods in Dittmann et al). 
Qualified patients started treatment as inpatients. After week 6, responders (Brief Psychiatric Rating Scale [BPRS]; improvement, ≥30%) continued as outpatients in an open-label extension (18 weeks). Outcome measures comprised: BPRS, Global Impression of Severity (CGI-S), CGI Improvement scale, a self-rated subjective well-being scale (SWN, 20-item short form; higher scores = better well-being), spontaneously reported treatment-emergent adverse events (TEAEs), the Udvall for Kliniske Undersogelser (UKU) side effects scale, weight, body mass index (BMI), vital signs. Olanzapine plasma levels and serum leptin levels were assessed. Treatment with olanzapine was adjusted within a dose range of 5 to 20 mg/d. Statistical methods have been described; subgroup analyses (2×3), for example, comparing male versus female (m/f) patient groups, were performed.

Data are based on 96 patients; 80 (83.3%) completed the 6-week acute study period, 60 (62.5%) were responders, 34 (35.4%) completed the 24-week study, 68 (70.8%) patients were male, mean age was 15.9 (± 1.4) years. Baseline mean BPRS total score was 39.2 (±13.4); 38.3 (±14.1) for males and 41.4 (±11.3) for females (P > 0.20). For males, the mean BL BMI was 20.9 (± 2.8); for females, 21.3 (± 4.0; m/f; P > 0.50). The mean olanzapine dose was 14.2 mg/d, of the highest dose 16.7 mg/d. Mean olanzapine plasma levels amounted to 47.8 (±24.1) ng/mL (n = 84) by week 6 and 42.2 (±24.8) ng/mL by week 24 (responders only, n = 56). The mean BPRS total score decreased from BL to week 6 by 17.0 (± 14.4; P = 0.001; N = 96), with a mean improvement of 43.1% (± 32.1%). No sex differences in mean change of BPRS total and positive and negative subscores were observed. A total of 62.5% of the patients (n = 60/96) met response criteria; rates were 60.3 (m) and 67.9% (f; m/f; P > 0.20). The rate of patients assessed as markedly ill or worse (CGI-S) declined from 83.3% (BL) to 37.5% (week 6; P < 0.001). There were no m/f differences in various CGI-S parameter changes (all P > 0.20). The SWN total scores increased from BL to week 6 (by 7.5 ± 16.4; P < 0.001) both in males (P < 0.001) and in females (P < 0.07). By week 24, mean SWN changes amounted to 11.9 (± 20.6; m) and 13.8 (± 20.6; f; m/f; P > 0.50). Significant correlations were observed (week 6), that is, investigator-rated BPRS total and CGI-S scores, r = 0.73 (P < 0.001); BPRS total and patient-rated SWN total scores, r = −0.24 (P = 0.032); and CGI-S and SWN total scores, r = −0.24 (P = 0.029).

There were 519 TEAEs documented in 89 (92.7%) patients; 268 (51.9%) were considered to be possibly related to olanzapine treatment. Most commonly reported TEAEs were weight gain (30.2%, 29/96) and increased prolactin (PRL) levels (25.0%, 24/96). Serious AEs were observed in 3 males (all “not related”). The TEAEs led to early discontinuation in 3 patients. No deaths were reported. Few significant m/f differences were found (UKU items, by week 6): females reported more “orthostatic dizziness” (P < 0.01), more of a reduction of “depression” and “tension headache” (both P < 0.05); males reported more weight gain (P < 0.10). Findings for changes in hematology and metabolic and liver function parameters have been published. Higher than normal BL serum PRL levels (Covance laboratory upper limit of normal range; Table 1) were found in 28.1% (27/96) of the patients, in 23.5% (m) and 32.1% (f; m/f; P > 0.20). By week 6, 70.8% showed elevated PRL levels and (responders only) 13.3% (8/60) by week 24. The respective m/f rates were 70.6% and 71.4% (by week 6, m/f; P > 0.20) and 12.2% and 15.8% (by week 24, P = 0.20). The maximum single PRL levels were 58 (m) and 104 µg/L (f; both found at week 6). For mean serum PRL levels, changes over time, and (selected) m/f results, cf. Table 1. The TEAEs (COSTART terms; N = 96) possibly associated with elevated PRL.
were gynecomastia 6.3%; decreased libido, 3.1%; female galactorrhea, 2.1%; and amenorrhea and breast pain 1.0% each. There were no discontinuations due to high PRL levels (one because of galactorrhea). At BL, there were no significant correlations, but by week 6, PRL levels correlated with weight \( (r = -0.30, P = 0.007) \) and maximum olanzapine doses \( (r = 0.34, P = 0.002) \).

Data on blood pressure and heart rate changes have been reported,\textsuperscript{13} with standing systolic \( (4.7 \pm 18.2 \text{ mm Hg}; P = 0.013) \) and diastolic mean blood pressure increases \( (3.4 \pm 14.2 \text{ mm Hg}; P = 0.023) \) from BL to week 6. For males, they were \( 5.4 \pm 18.4 \text{ mm Hg}; P = 0.034 \) and \( 4.0 \pm 14.9 \text{ mm Hg}, P = 0.019 \), and for females (not significant [n.s.]), \( 3.1 \pm 18.0 \) and \( 2.0 \pm 12.4 \text{ mm Hg} \). Sex differences in mean changes of blood pressure and heart rate were minor (n.s.). No significant changes from BL to week 24 were seen in vital signs. Mean weight gain and BMI findings have also been reported.\textsuperscript{13} The highest single leptin level was 77.0 \( \mu \text{g/L} \) at week 24. For the entire population, mean leptin levels increased from BL \( (5.8 \pm 8.2 \text{ to week 6, 9.8 } \pm 10.7, n = 81, \text{ to week } 24, 13.7 \pm 15.7 \text{ \mu g/L}, n = 46) \). Mean BL levels were found at \( 2.5 \pm 2.7 \text{ (m, n = 63) and } 16.4 \pm 12.3 \text{ \mu g/L}, (f, n = 24; m/f; P < 0.001). At week 6, they were observed higher in both sexes \( (5.8 \pm 5.5; m, n = 54 \text{ and } 22.6 \pm 12.8 \text{ \mu g/L}; f, n = 25; m/f; P < 0.001). \) The respective findings for week 24 were \( 8.2 \pm 7.6; n = 25 \) and \( 37.1 \pm 25.9 \text{ \mu g/L (n = 7; m/f; P < 0.001). All across visits, there were no significant correlations between leptin levels and current olanzapine dose \( (P = 0.61) \) or body weight \( (P = 0.99) \). The respective correlation between weight and current olanzapine dose was \( r = 0.18 \ (P < 0.001). \)

**DISCUSSION**

This comparatively large 24-week study of oral olanzapine in 96 adolescent patients allowed for secondary comparisons of male and female patients with respect to various selected parameters of effectiveness and tolerability including, for example, subjective well-being and PRL levels. In earlier studies with smaller samples, m/f comparisons had hardly been performed.\textsuperscript{9,11,12} Two placebo-controlled studies with olanzapine in adolescents after this one plus a summary article on safety have been published.\textsuperscript{10,14,15} Overall, despite effectiveness for a number of outcome parameters, hardly any statistically significant sex differences were found in this study (with a few minor exceptions).

For the entire sample, a statistically significant mean BPRS\textsubscript{S0-6} total improvement was observed (>60% response rate) with female patients showing (n.s.) slightly higher scores in some BL BPRS scores and improvements by week 6. This also held for response rates, CGI-S scores, and rates of “improved” patients. Findings were in line with results from 6-week studies in adult patients.\textsuperscript{8} In addition, SWN total scores improved, for all, male and female, patients by week 6. In contrast to the investigator-rated BPRS and CGI scores, both males and females reported further SWN improvement up to week 24. Correlations suggested additional value in patient-rated outcomes, with potential impact on patient compliance. Most commonly reported adverse events were weight gain and an increase in PRL blood levels. Based on UKU data, very few sex differences in adverse event rates were reported. For mean PRL blood levels, we observed statistically significant sex differences at BL and weeks 6 and 24. These values increased by week 6 corresponding to even clearer sex differences reported for adults; and rates of treatment-emergent elevated PRL levels also seemed to be higher compared with adult patients both in males and females.\textsuperscript{3,13,19} Importantly, for responders, up to week 24, mean PRL levels seemed to return to normal ranges (both in m/f). Potential clinical relevance and long-term impact of elevated PRL levels and related AE's remain to be determined, in close collaboration with pediatric endocrinology. Limitations to be considered include: open-label design; no comparisons with other antipsychotics; initial hospitalization; use of benzodiazepines; olanzapine dose not fixed; beyond week 6, results valid for responders only; 64.6% of patients not completing the 24-week study (in line with dropout rates found in adults\textsuperscript{20}); sample sizes of m/f subgroups relatively small; sex comparisons done post-hoc, not controlled for multiplicity, on selected items, in an exploratory approach.

In summary, olanzapine treatment in adolescent patients with schizophrenia was associated with significant improvements on several measures of effectiveness. Changes in weight and prolactin levels were greater than has been reported in adult patients, in line with Kryzhanovskyakaya et al.\textsuperscript{15} Sex differences in general did not reach statistical significance. Some results (n.s., but consistently) seemed to favor female patients and may correspond to the notion of “superior treatment response” in females.\textsuperscript{7} In addition, olanzapine treatment seemed effective in improving subjective well-being. Investigation into long-term outcomes is recommended, also replication, with greater attention to the impact of estrogen in general, to pharmacokinetics in females, and to neuroendocrine adverse events. In conclusion, effectiveness and tolerability data from this trial suggest that—with consideration of the potential risks—olanzapine treatment may be a treatment option for adolescent patients with schizophrenia. These findings were supported by 2 recent placebo-controlled trials in adolescents,\textsuperscript{10,14} but olanzapine has not yet been approved by regulatory agencies for use in this patient population.

**ACKNOWLEDGMENTS**

The authors thank Drs F. Beer, T. Boretsch, M. Dupont, M. Einig, C.

AUTHOR DISCLOSURE INFORMATION
This research was supported by Lilly Deutschland GmbH, Bad Homburg, Germany. Contributors: R.W. Dittmann designed the study and wrote the protocol and the manuscript. U. Hagenah, J. Junghanss, A. Mästele, F. Poustka, H. Remschmidt, M.H. Schmidt, and E. Schulz were involved in the conceptualization level and contributed to the design of the study. A. Mästele and R.W. Dittmann coordinated the research. M. Kluge (then employee of Lilly Germany) supported data management and analyses of the study. F.J. Freisleder, U. Hagenah, J. Junghanss, C. Mehler-Wex, E. Meyer, F. Poustka, H. Remschmidt, M.H. Schmidt, E. Schulz, and FM. Wohmeier (before joining Lilly Germany as an employee) contributed to patient enrollment and data collection at the study site level. All authors contributed to and have approved the final manuscript. Conflict of interest: A. Mästele, and PM. Wohmeier are full-time employees of Lilly Deutschland GmbH. Ralf W. Dittmann is a former employee and stock holder of Lilly Deutschland GmbH. M. Schulte-Markwort has received support from Lilly Deutschland GmbH (consulting fees, speaker’s bureau, grant/research support). E. Meyer, F. Poustka, and M.H. Schmidt have received support from Lilly Deutschland GmbH (speaker bureau, grant/research support). F.J. Freisleder, U. Hagenah, J. Junghanss, C. Mehler-Wex, H. Remschmidt, and E. Schulz have received support from Lilly Deutschland GmbH (grant/research support).

Ralf W. Dittmann, MD, PhD
Eli Lilly Endowed Chair of Pediatric Psychopharmacology
Department of Child and Adolescent Psychiatry and Psychotherapy
Central Institute of Mental Health Mannheim
University of Heidelberg
Mannheim, Germany
ralf.dittmann@zi-mannheim.de

Eberhard Meyer, MD
Hospital for Child and Adolescent Psychiatry and Psychotherapy
Riedstadt, Germany

Franz Joseph Freisleder, MD
Hecksher-Hospital for Child and Adolescent Psychiatry and Psychotherapy
Munich, Germany

Helmut Remschmidt, MD, PhD
Department of Child and Adolescent Psychiatry and Psychotherapy
University of Marburg
Marburg, Germany

Claudia Mehler-Wex, MD
Department of Child and Adolescent Psychiatry and Psychotherapy
Children’s Hospital Josefimun
Augsburg, Germany

Ulrich Hagenah, MD
Department of Child and Adolescent Psychiatry and Psychotherapy
University Hospital Aachen
Aachen, Germany

Jenny Junghanss, MD
Department of Child and Adolescent Psychiatry and Psychotherapy
Children’s Hospital Josefimun
Augsburg, Germany

Ulrich Hagenah, MD
Department of Child and Adolescent Psychiatry and Psychotherapy
Children’s Hospital Josefimun
Augsburg, Germany

Michael Schulte-Markwort, MD
Department of Child and Adolescent Psychiatry and Psychotherapy
University of Hamburg
Hamburg, Germany

Fritz Poustka, MD
Department of Child and Adolescent Psychiatry and Psychotherapy
J.W. Goethe University
Frankfurt, Germany

Eberhard Schulz, MD
Department of Child and Adolescent Psychiatry and Psychotherapy
University of Freiburg
Freiburg, Germany

Michael Kluge, MD
Max Planck Institute of Psychiatry
Munich, Germany

Anneliese Mästele, MS

Peter M. Wohmeier, MD
Division of Neuroscience
Medical Department
Lilly Deutschland GmbH
Bad Homburg, Germany

Martin H. Schmidt, MD, PhD
Department of Child and Adolescent Psychiatry and Psychotherapy
Central Institute of Mental Health Mannheim
University of Heidelberg
Mannheim, Germany

REFERENCES
Birth Weight and Use of Olanzapine in Pregnancy: A Prospective Comparative Study

To the Editors:

Whereas teratogenicity has received much attention, relatively few studies have examined other effects of atypical antipsychotic agents on pregnancy and the fetus, although these medications diffuse readily across the placenta. Clozapine and olanzapine have been associated with metabolic disorders such as obesity, dyslipidemia, and diabetes mellitus. Pregnancy itself is considered as a stressful period and may uncover impaired glucose tolerance resulting in diabetes mellitus. In a study on placental passage of newer atypical antipsychotic agents, placental passage ratio was maximum for olanzapine, followed by haloperidol and risperidone, and lowest for quetiapine. Recent studies do not indicate an association between atypical antipsychotic agents and major malformations, but there have been mixed results regarding the effect of atypical antipsychotic agent use in pregnancy on gestational age and birth weight. One study reported an increased risk of low birth weight and neonatal intensive care unit admissions among pregnant women with olanzapine exposure exceeding population norms. However, another study reported that pregnant women exposed to atypical antipsychotic agents had a significantly higher incidence of large-for-gestational age infants compared with those exposed to typical antipsychotic agents. The study sample here was small (n = 25) and was collected over 11 years and may have not accounted for time-related changes in birth weights. We hypothesized that olanzapine use during pregnancy results in increased infant birth weight and larger-for-gestational age infants in women exposed to the medication compared with those exposed to other psychotropic medications. To study this, a prospective observational study was conducted comparing birth weight and gestational age of infants exposed to olanzapine with those of a group exposed to other psychotropic medications.

The subjects included 70 pregnant women who were exposed to olanzapine and other psychotropic medications during gestation from the year 2005 to 2009, attending the perinatal psychiatry clinic at the National Institute of Mental health and Neurosciences, Bangalore, India. These women were regularly followed up till delivery and were seen at the earliest week after delivery. Data collected from the pregnant women and the primary care taker included sociodemographic details, past obstetric history, personal or family history of diabetes mellitus, or gestational diabetes mellitus. Childbirth details included gestational age, nature of delivery, obstetric complications, and Apgar score. Birth weight and infant details were based on information provided by the relatives and hospital records at the time of delivery. Dose and timing of exposure to psychotropic medications with respect to conception were collected. Clinical diagnosis was made by a consultant psychiatrist by using the International Statistical Classification of Diseases, Tenth Revision. Informed consent was obtained from all mothers, and because this data was collected as part of routine clinical care, specific ethics committee approval was not considered. Among the 70 women, 18 subjects (28%) did not come for a further follow-up, whereas 2 women underwent medical termination of pregnancy and 2 women had abortions. Only infants born at full term (37–42 completed weeks of gestation) with a record of birth weight were included in the final analysis. Two women with polyhydramnios, 1 woman with a preterm delivery, and 1 infant with meconium were excluded. The infant outcome assessed in this study was birth weight, which was not available for 7 infants who were excluded. An independent t test was used to compare groups with women using olanzapine, olanzapine with other psychotropic medications, and psychotropic medications other than olanzapine. Birth weight was normally distributed in the sample for analysis. Finally, 37 pregnant women treated with psychotropic medications during pregnancy were included for the analysis. The mean (SD) age of these women was 26.3 (4.98) years. All women were married, and 22 women (59.5%) were primigravidas. The primary psychiatric diagnoses are described in Table 1. Fasting blood glucose levels were available for 17 women (45.9%) before conception and 6 women (16.2%) during gestation. Blood glucose levels were lower than 115 mg/dl in all women. Two women (5.7%) had a family history of diabetes mellitus. None of the women had a history of any substance abuse. Among the 37 women, 18 (48.6%) underwent cesarean delivery, and among them 12 (66.6%) were emergencies. The rest had normal-term vaginal deliveries. Four women (11%) had infants with fetal hypoxia during labor and hence underwent emergency cesarean delivery. The study group included 2 subgroups: the first group consisted of 12 infants exposed to olanzapine monotherapy; and the second, 12 infants exposed to olanzapine with other psychotropic medications. The control group included 13 infants whose mothers were exposed to psychotropic medications other than olanzapine. The mean dose (P = 0.65) and duration (P = 0.49) of olanzapine were not significantly different between the 2 test subgroups (Table 1). The mean (SD) gestational age was 37.52 (0.69) weeks, and the mean (SD) weight of the infants was 3075.6 (371.2) gm. The mean (SD) infant weight in the olanzapine monotherapy group was 3310 (333.1) g, with 1 infant having a birth weight of 4000 g. The mean weight in the olanzapine polytherapy group was 3008 g, and that in the control group was 2921 g (Table 1). Comparison using analysis of variance showed significantly higher weight among infants in the olanzapine monotherapy group (P = 0.02) when compared with the other groups. Post-hoc analysis showed significantly higher birth weight among the olanzapine monotherapy group (n = 12) compared with the olanzapine polytherapy group (n = 12, P = 0.037).

DISCUSSION

The current study reports initial data on the relationship between olanzapine use in pregnancy and infant birth weight. The results of this study suggest that exposure to olanzapine only during pregnancy may be associated with higher birth weight when compared with use of other psychotropic medications during pregnancy. The only earlier study on this topic...
TABLE 1. Clinical Characteristics of Pregnant Women and Infant Birth Weight

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olanzapine Group (n = 12)</th>
<th>Olanzapine Plus (n = 12)</th>
<th>Non-Olanzapine (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>27.91 (5.79)</td>
<td>25.25 (4.67)</td>
<td>26.0 (3.94)</td>
</tr>
<tr>
<td>Gravida</td>
<td>1.58 (0.90)</td>
<td>1.36 (0.67)</td>
<td>1.63 (1.12)</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>6</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Olanzapine dose, mg</td>
<td>11.0 (4.4)</td>
<td>10.2 (4.5)</td>
<td>—</td>
</tr>
<tr>
<td>Olanzapine use, wk</td>
<td>31.5 (9.82)</td>
<td>28.4 (9.4)</td>
<td>—</td>
</tr>
<tr>
<td>Infant birth weight, g</td>
<td>3310.0 (333.2)*</td>
<td>3008.3 (366.1)</td>
<td>2921.5 (323.2)</td>
</tr>
</tbody>
</table>

*P = 0.02.

Letters to the Editors

Journal of Clinical Psychopharmacology • Volume 30, Number 3, June 2010

using a control group showed higher birth weight in women using atypical antipsychotic agents, particularly with olanzapine and clozapine. In our study, infants of women on olanzapine monotherapy had higher propensity for increased birth weight when compared with other psychotropic use or exposure to a combination of olanzapine with other psychotropic medications. This was not explained by the dose difference or the duration of use of olanzapine in the 2 groups. Differences in birth weight were also not attributable to gestational age, maternal age, or the infant sex in the sample. However, a larger sample with maternal weight and maternal blood glucose may give us a better understanding of the relationship between olanzapine and infant birth weight. The only infant in the sample who had macrosomia (>4 kg) was in the olanzapine monotherapy group. Based on population data, the birth weight of infants born to women without any physical or mental illness in both urban and rural southern India is approximately 2500 to 3000 g. Compared with this, the birth weight of the olanzapine-exposed infants in our study (which was done in a similar population) is higher by 300 to 400 g. Approximately 48% of the women in our sample underwent cesarean delivery, two thirds of whom underwent an emergency cesarean delivery. Reasons for emergency cesarean delivery were not available in majority of cases, and in few cases the reason was fetal hypoxia. The implications of infant weight gain on mode of delivery need further evaluation. The main limitations of the current study include (1) lack of information on maternal weight and blood glucose levels in the mother, which would have given better understanding in their role in infant birth weight; (2) reliability of birth weight recording, as birth weights were recorded by the health centre or hospital where the woman delivers, and we had to rely on these data; and (3) having a control group not on psychotropic medication would have reduced the influence of some of the confounding factors. The important strengths have been that the sample was prospective and the data was collected for 4 to 5 years. Hence, the cohort effects due to longer period of study are minimal, which may influence the nutritional status and type of the drug used. We also had detailed reliable records of dose and duration of exposure to medication. This study supports the possible association between in utero exposure of olanzapine and increased birth weight in infants. However, results need to be replicated with larger samples.

AUTHOR DISCLOSURE INFORMATION

The authors declare no funding or conflicts of interest.

Girish N. Babu, MD
Geetha Desai, MD, DNB
Harish Tippeswamy, MD
Prabha S. Chandra, MD, MRCPsych
Department of Psychiatry
National Institute of Mental Health and Neurosciences
Bangalore, India
chandra@nimhans.kar.nic.in; prabhusch@gmail.com

REFERENCES

The Prevalence of Tardive Dyskinesia in Chinese Singaporean Patients With Schizophrenia Revisited

To the Editors:

Tardive dyskinesia (TD) is a form of neuroleptic-induced disorder characterized by choreoathetoid or other involuntary movements. Tardive dyskinesia has been shown to increase mortality and is associated with a more severe and treatment refractory illness course. The current management strategy lies in the prevention of TD onset. An earlier study by Chong et al in a Southeast Asian population had reported prevalence of TD to be as high as 40.5%. In this study, we sought to recruit an independent sample of Chinese Singaporeans with schizophrenia to establish the point prevalence of TD and examine the risk factors associated with it. In addition, we will compare the findings of this study with an earlier study in 2001 and examine any changes in the rates and the associated factors. We hypothesize that the rate will generally be lower owing to the greater use of atypical neuroleptics in the intervening years.

This study was conducted at the Institute of Mental Health (IMH) in Singapore, the only psychiatric hospital in the country. Seven hundred ninety-nine patients with schizophrenia were recruited for this study during the period 2005 to 2008 and comprised a mixture of both inpatients and outpatients. Patients with a diagnosis of schizophrenia and of Chinese ethnicity were eligible for this study. They were excluded if they had organic brain disorders, epilepsy, or mental retardation. This study was approved by the institutional review board. Only subjects capable of providing written informed consent were recruited for this study. Extensive data collection forms were used in the gathering of information. Current neuroleptic doses were converted into total daily chlorpromazine equivalents. Diagnosis of schizophrenia was made using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Research Version, Patient Edition, and psychological symptoms were rated using the Positive and Negative Syndrome Scale (PANSS). Dyskinesia was rated on the Abnormal Involuntary Movement Scale. Patients were defined as having TD if they fulfilled the Schooler and Kane criteria, namely, movements were “mild” in at least 2 body regions or were rated as “moderate” in at least 1 body region, and with at least 3 months of neuroleptic treatment. Extrapyramidal side effects (EPS) were assessed on the Simpson-Angus Rating Scale. Positive EPS status was defined by a total Simpson-Angus Rating Scale score of 3 or higher. These assessments were performed by trained clinicians who were blinded to the clinical history of the patients and who had established inter-rater reliability with a k < 0.8. All statistical analyses were performed using Stata SE 10.0 (StataCorp, TX). Descriptive statistics were calculated and model building was performed using a purposeful selection algorithm suggested by Hosmer and Lemeshow. The adjusted odds ratios, 95% confidence intervals, and P values were subsequently computed from the final model.

The demographic and clinical characteristics of the 790 recruited patients are shown in Table 1. One hundred sixty-six (21.0%) patients were assessed to have TD, and 228 (28.9%) were assessed to be positive for EPS. The median total daily chlorpromazine equivalent dose was 312.5 mg/d (interquartile range, 143–594 mg). The patients with TD were older and had a longer duration of neuroleptic exposure. There was a higher proportion of diabetes mellitus and EPS-positive status in the group of patients with TD. There were no statistically significant differences between distributions of sex, body mass index, and smoking status. The patients with TD received a lower total daily chlorpromazine equivalent dose, and a smaller proportion of them were on atypical neuroleptics. There were no differences in the proportions of antidepressant, anticholinergic, benzodiazepine, or mood stabilizer usage between the TD and non-TD groups. There were no significant differences between the PANSS total and subscale scores between the 2 groups. The regression model consisted of 8 variables: age, duration of cumulative neuroleptic exposure, diabetes mellitus, current neuroleptic dose, anticholinergic use, EPS status, PANSS negative, and general psychopathology score. Age (P < 0.001) and EPS status (P < 0.001) emerged as significant factors in the prediction of TD status. The risk of TD was higher with increasing age, and this risk rose significantly for those aged 60 years or older (odds ratio, 12.2; confidence interval [CI], 5.43–27.3). The presence of EPS was associated with an odds ratio of 3.14 (CI, 2.08–4.74) of TD.

DISCUSSION

The prevalence of TD in Chinese Singaporeans with schizophrenia was 21.0% as shown in this study. Increasing age and the presence of EPS were associated with increased risk of TD in our population in the multivariate analyses. As predicted, the prevalence of TD obtained in this population was lower than the 40.5% obtained in an earlier study in 2001 reported by Chong et al. The lower mean age, higher atypical neuroleptic usage, and lower neuroleptic dose could have explained the lower TD rates in this study.

Our study concurred with the earlier study by Chong et al that increasing age was a significant risk factor. This finding is consistent with reports from other international groups from different ethnic populations. Our study showed a trend toward significance with higher current neuroleptic dose associated with lower rates of TD. Higher doses of neuroleptics could have masked features of TD and led to the observed lower rates of TD. This finding could also be an artifact from the cross-sectional study design. Neuroleptic doses could have been reduced during clinical management of the patients with TD and EPS.

We found that the group without TD had a higher proportion of atypical neuroleptic usage. However, there was no significant difference in proportion of typical neuroleptic prescribed between the TD and non-TD groups. Again, the cross-sectional design did not permit us to establish the temporal relationship between the onset of TD and the use of typical and atypical neuroleptics. Prevalent cases of TD could have been identified earlier by their treating clinicians, with consequent downward adjustment of neuroleptics and a switch to atypical neuroleptics with a supposed lower risk. We found the presence of EPS to be a significant risk factor for TD. Some studies have reported that EPS is associated with increased risk of subsequent TD. This could be due to the sensitivity of the basal ganglia system to dopaminergic antagonism, but the exact mechanism is not well understood.

Unlike studies from other ethnic groups, our study replicated earlier findings from Chong et al and Schultz et al that diabetes mellitus and hyperglycemia were not significant risk factors for TD in Chinese Singaporeans. We did not find any sex difference in the risk of TD. This could be due to the older mean age of the population and the long duration of cumulative neuroleptic exposure. These 2 factors might have overwhelmingly influenced the risk of TD and masked the effect of sex. Contrary to other studies, smoking was not a significant risk factor in our study. Inpatients in our hospital have no access to cigarettes upon admission and will not be able to smoke. Institutionalized
<table>
<thead>
<tr>
<th>TABLE 1. Distribution of Variables Between Patients With TD and Those Without TD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
</tr>
<tr>
<td><strong>n = 790</strong></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
</tr>
<tr>
<td><strong>Cumulative neuroleptic exposure, y</strong></td>
</tr>
<tr>
<td><strong>Current neuroleptic dose, mg</strong></td>
</tr>
<tr>
<td><strong>PANSS score</strong></td>
</tr>
<tr>
<td><strong>Positive</strong></td>
</tr>
<tr>
<td><strong>Negative</strong></td>
</tr>
<tr>
<td><strong>General psychopathology</strong></td>
</tr>
<tr>
<td><strong>n (%)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Current smokers</strong>&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>EPSE</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td><strong>Typical neuroleptic</strong></td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
</tr>
<tr>
<td><strong>Atypical neuroleptic</strong></td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong>&lt;sup&gt;∥&lt;/sup&gt;</td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
</tr>
<tr>
<td><strong>Mood stabilizers</strong>&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Absent</td>
</tr>
</tbody>
</table>

*Student t test.
†Current neuroleptic doses were converted into total daily chlorpromazine equivalents.
§Number of subjects (proportion).
∥χ² test.

Patients could have a more severe course of illness and are exposed to larger doses of neuroleptics. Therefore, they could be at higher risk of TD even without smoking.

The large numbers of Chinese patients assessed within a single site with standardized instruments, and accurate phenotyping of schizophrenia with structured instruments are the strengths of this study. This study population was analyzed separately from the earlier reported study on 537 Chinese patients and acted as a validation sample to elucidate risk factors for TD in the same population. This study has several limitations, most of which are inherent in the cross-sectional study design as discussed earlier. We did not examine risk factors for subtypes of TD, such as persistent TD or TD affecting specific regions only. We were not able to establish the time of TD onset, or the total cumulative neuroleptic dose exposed. Although there was no information on spontaneous dyskinesia in this study population and its impact on TD development, a separate study on 691 Chinese patients with first-episode psychosis did not identify anyone with spontaneous dyskinesia. Diagnosis of diabetes mellitus was based on clinical records, and nondifferential misclassification of undiagnosed cases could have occurred.

In conclusion, our study found a fairly high prevalence of TD in Chinese Singaporeans with schizophrenia. Significant risk factors of TD in this population were age and presence of EPSE. Further, it suggests that more prevalent use of atypical neuroleptics is associated with a lower rate of TD. Future studies on TD should include pharmacogenetic biomarkers that provide additional information and dimension to TD risk factor research.

**ACKNOWLEDGMENT**

Funding for this study was provided by the National Medical Research Council, Singapore (NMRC). The NMRC had no further role in the study design; collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

**AUTHOR DISCLOSURE INFORMATION**

The authors declare no conflicts of interest.

Jimmy Lee, MMed (Psychiatry), Institute of Mental Health/Woodbridge Hospital Singapore jimmy.lee@imh.com.sg

Jundong Jiang, BSc (Hons) Institute of Mental Health/Woodbridge Hospital Singapore, Singapore and Integrative Science and Engineering National University of Singapore Singapore

Kang Sim, MMed (Psychiatry), FAMS Siow-Ann Chong, MMed (Psychiatry), MD, FAMS Institute of Mental Health/Woodbridge Hospital Singapore
Clozapine-Associated Cerebral Venous Thrombosis

To the Editors:

Clozapine, an atypical antipsychotic agent used to treat refractory schizophrenia, is well known to cause agranulocytosis, a potential fatal adverse effect in about 1% to 2% of patients. There are also several reports of cardiomyopathy with clozapine treatment, but little attention has been drawn to thromboembolic complications of clozapine use. Commonly reported thromboembolic phenomena are pulmonary embolism and peripheral venous thromboembolism.2,3 To the best of our knowledge, there is only 1 previous report of cerebral venous thrombosis (CVT) in patients undergoing clozapine treatment to date.4 We report a patient who developed CVT while on clozapine treatment. Because CVT is a potentially life-threatening complication, clinicians have to be alert to this rare complication.

CASE REPORT

Ms X., a 30-year-old unmarried woman, a graduate in computer engineering, with chronic paranoid schizophrenia of 15 years’ duration consulted our emergency clinical team in January 2009 with a 5-day history of irritability, episodes of vomiting, increased fatigability, and poor personal care. General physical examination revealed hemiparesis of the left upper and lower limbs. There were no signs of increased intracranial pressure. Mental state evaluation revealed no worsening of psychotic symptoms, with normal cognitive functions and intact sensorium. She had been previously treated with trifluoperazine, flupentixol, olanzapine, risperidone, and amisulpride for many years without any satisfactory improvement. For the previous 3 years, she has been on clozapine 400 mg/d as she had not responded to other antipsychotic drugs. Her symptoms reduced significantly with clozapine, but she developed 1 episode of seizure for which she was treated with sodium valproate 400 mg/d without any recurrence of seizure attacks. She has been on sodium valproate for the previous 2 years. No other medications were given.

Computed tomography scan of the brain revealed hyperdense right transverse sinus and straight sinus with empty delta sign in the posterior superior sagittal sinus on contrast enhancement. Magnetic resonance venography (Fig. 1) showed evidence of thrombosis involving superior and inferior sagittal sinus, right transverse sinus, and right jugular bulb. Hemogram results were within normal limits: total white blood cell count was 9200 cells/μL, of which 60% were neutrophils and 30% were lymphocytes. Platelet count was 300,000 cells/μL. Complete evaluation for systemic vasculitis was negative including rheumatoid arthritis factor, antinuclear antibodies, antiphospholipid antibodies (immunoglobulins M and G), and lupus anticoagulant. A complete coagulation profile was done, which concluded normal values of fibrinogen levels, antithrombin III activity (93% [70%–122%]), and factors VIII (64% [60%–150%]) and IX (61% [60%–150%]) activity. Factor V Leiden mutation (R506Q substitution) and factor II (prothrombin gene [G20210A]) mutation detection by real-time polymerase chain reaction techniques yielded negative results. Plasma proteins C and S activity levels while on anticoagulation therapy were low, 31% (67%–195%) and 32% (55%–123%), respectively. Urine homocysteine levels were within normal limits. Renal, liver, and thyroid function tests were also within normal limits. Smoking, cancer, dehydration, oral contraceptive use, pregnancy, surgery, trauma, immobilization, sedation, sedentary life style, immunologic abnormalities, connective tissue disorders, factor V Leiden, and factor II prothrombin mutations are the usual risk factors leading to venous thrombosis.5,6 Our patient led a sedentary life, but none of the other risk factors were present in her.

Anticoagulation therapy was initiated initially with heparin 5000 IU QID and subsequently substituted with nicoumalone.

REFERENCES


FIGURE 1. Magnetic resonance venography showing thrombosis of the superior and inferior sagittal sinus, right transverse sinus, and right jugular bulb.
Although venous thromboembolism is dose dependent occurring mainly in the first 3 months of clozapine treatment, 1 patient reported in the Swedish registry developed deep vein thrombosis after treatment duration of 2 years. Possible mechanisms for the association between clozapine and venous thromboembolism are probably multifactorial, usually occurring when 1 of 3 factors is present: damage to the vessel wall, static blood flow, or coagulation abnormalities. Clozapine has not been shown to cause direct damage to the vasculature, but static blood flow may be influenced by sedation and sedentary lifestyle commonly associated with psychiatric disorders, their treatment, or both. However, whether clozapine is a prothrombotic agent is not clear. Two studies suggest that clozapine inhibited platelet aggregation induced by adenosine diphosphate and collagen, whereas another study suggested that clozapine increased platelet adhesion, although weakly.

It has been suggested that the thromboembolic complications in patients using clozapine can be largely attributed to presence of coagulation abnormalities such as factor V Leiden and factor II mutations. In our patient, there seems to be no obvious risk factors for the occurrence of CVT as investigations evaluating coagulation profile and immunologic risk factors were negative. Low plasma proteins C and S activity levels are observed due to initiation of anticoagulation therapy. In addition, there were no other risk factors such as smoking, dehydration, oral contraceptive use, pregnancy, surgery, trauma, and immobilization. Because the patient also received sodium valproate 400 mg/d, one could argue that the CVT may be attributed to it. We think it is an unlikely cause because our coagulation workup did not reveal any abnormalities and valproate is known to induce abnormalities in coagulation factors. Moreover, valproate is known to induce both procoagulation and anticoagulation factors; therefore, that valproate may cause thrombotic events is equivocal. Considering the absence of known risk factors, there is a possibility that clozapine use alone may have contributed to the development of CVT. The fact that CVT occurred years after initiation of clozapine therapy in the absence of obvious risk factors has important clinical implications. Clinicians have to be alert to the possibility of CVT being a complication of clozapine therapy, which may necessitate its withdrawal. Finally, it is also worth highlighting that this treatment-resistant patient was successfully transitioned from clozapine to aripiprazole as she maintained her clozapine-induced improvement when clozapine was switched to aripiprazole.

**DISCUSSION**

There are no conflicts of interest for any of the authors. There were no sources of support for this study.

**AUTHOR DISCLOSURE INFORMATION**

There are no conflicts of interest for any of the authors. There were no sources of support for this study.

**REFERENCES**

schizophrenia (including childhood-onset schizophrenia)\textsuperscript{1,2} and in patients who have severe neurological adverse effects with other antipsychotics. This treatment can be considered for poorly responding first-episode psychosis.\textsuperscript{3} Despite a higher incidence of hematologic adverse events, clozapine seems to be a uniquely beneficial third-line agent for treating children and adolescents with refractory schizophrenia.\textsuperscript{4} Although clozapine can induce agranulocytosis, the risk of this adverse effect exponentially decreases over time, with an incidence of 0.70 per 1000 patient-years in the second 6 months of treatment and 0.39 per 1000 patient-years after the first year. The case-fatality rate of clozapine-induced agranulocytosis is estimated as 4.2% to 16%.\textsuperscript{4} Clinical studies have reported higher rates of neutropenia in children and adolescents treated with clozapine than in adults, but agranulocytosis has no similar correlation with age.\textsuperscript{1,2} A baseline absolute neutrophil count of less than 2000/µL could be a predictor of risk of developing neutropenia,\textsuperscript{5} justifying the regular close controls.

We report a case that demonstrates the use of clozapine in a teenager presenting refractory first-episode psychosis with neutropenia: a 15-year-old white boy was admitted to the psychiatric department with behavioral disorders. He is the youngest of 3 siblings. He was in the fifth year of secondary school while a breakdown in his performance was observed. Six months before admission, his parents reported symptoms such as sadness and social withdrawal; more recently, he presented irritability, agitation leading to physical conflicts, oddness noticed by his teachers with inappropriate laughter, thought blocking, and concentration disorder. He was described as solitary, with few relationships and an affinity for video games. Neither prior psychiatric history nor medical history was reported. There is a family history of psychiatric disorders, including a schizophrenia and anorexia nervosa in paternal cousins. During his hospitalization, the patient experienced frequent neurological dystonia-like movements of the neck and somatic delusions (feelings of voluminous organs, including lungs, heart, and brain, as well as feelings of organ theft). Preoccupations with computer games and fantasy stories, auditory hallucinations (film actors’ voices), jovial mood, and behavioral disinhibition, such as kissing medical staff and using lewd speeches, were observed.

Results of the physical examination and other investigations (blood tests, electroencephalogram, computerized tomography, and brain magnetic resonance imaging) were considered normal with, however, an absolute neutrophil count of 1690/µL. The possibility of substance abuse was eliminated. Neuropsychological assessments did not show any disturbance in executive functions. The structural personality interview (Minnesota Multiphasic Personality Inventory, Rorschach) suggested high scores on the introversion scale with lack of self-confidence. The IQ tests were consistent with an average intellectual level.

As a first psychotic episode was considered, antipsychotics were prescribed but were unsuccessful. The patient first received various atypical and then conventional antipsychotics at efficient doses (risperidone 1–6 mg, olanzapine 10–20 mg, loxapine 100 mg, haloperidol 4–20 mg). Antipsychotics were tried for 6 weeks, on average, and were given concurrently with a mood stabilizer (lithium, valproamide) and/or sedative drugs (carbamate, alimemazine, or cyamemazine) in case of agitation, sleep disorders, or major anxiety. Regular blood counts were made because of the fortuitous discovery of the minor neutropenia. More pronounced neutropenia (1320/µL) associated with a decrease in red blood cells and platelets was noted during carbamate use. All psychotropic drugs had to be stopped because of the persistence of pervasive symptoms and/or adverse events, including weight gain and sedation. Consequently, clozapine was prescribed with parental consent while the neutrophil count was normal (2210/µL). However, clozapine was interrupted after 8 days because of a decrease in neutrophils (1650/µL). After a normalization of neutrophils, another clozapine administration was rechallenged but interrupted again after 3 days because of a decrease in neutrophils from 2110 to 1650/µL. During the following 6 weeks, he received another course of antipsychotics (amisulpride 800–1200 mg and zuclopenthixol) and was admitted to a psychiatric intensive care unit because of aggressiveness. Four months later, given the refractory psychosis, clozapine and electroconvulsive therapy were discussed. As considerable overnight fluctuations of the patient’s white blood count were noted, the assumption of an excessive margination of neutrophils with no toxic medullar mechanism was raised and allowed us to rechallenge clozapine after referring to a hematology specialist. Progressively, symptoms significantly improved; disinhibition and incongruous laughter progressively disappeared. After 1 year of clozapine treatment, the patient joined day psychiatric hospital with 4 hours of private lessons per week, and 6 months later, he returned to school. Psychotic symptoms disappeared completely. He presented with neither neurological adverse effects nor weight gain. The patient’s neutrophil count remained greater than 1700/µL at the time during clozapine treatment and even normalized after 6 months. Other blood lineages were also normal.

This teenager with a first psychotic episode did not respond to the usual antipsychotics and benefited from clozapine despite neutropenia. The use of clozapine is very restricted because of adverse events, including neutropenia, agranulocytosis, metabolic adverse effects, intestinal occlusion, and myocarditis. The use of clozapine at the first psychotic episode has been described, but its efficacy remains controversial.\textsuperscript{6,7,9}

In the present case, despite the low neutrophil count, clozapine was prescribed under hematologic and metabolic supervision. During the first treatments with antipsychotics, the addition of carbamate might have contributed to a decrease also in the red blood cells and platelets. Afterward, these modifications had not been observed while clozapine alone was prescribed. According to WhISkey and Taylor,\textsuperscript{9} the exact mechanism by which clozapine induces neutropenia and agranulocytosis is still uncertain. However, bone marrow suppression by clozapine could have an allergic hypersensitivity etiology\textsuperscript{10} (which, unlike in the case of carbamazepine, is not a toxic effect). One hypothesis is that clozapine can target stromal cells, central components of the bone marrow microenvironment that have been implicated in neutrophil development or involve peripheral destruction of cells.\textsuperscript{11} The white blood cell fluctuations and particularly the neutrophils in the present case could not be attributed to clozapine, because neutrophil synthesis in the bone marrow takes about 10 days. Circadian variations in the number of circulating neutrophils such as morning pseudoneutropenia might be evoked.\textsuperscript{12,13} However, as the fluctuations were noted from one day to another while blood samples were taken in the morning, the hypothesis of an excessive margination of neutrophils was raised. This hypothesis led to increase the benefit-risk ratio with the rechallenging of clozapine treatment. Besides an excessive margination of neutrophils or a morning pseudoneutropenia, it should not be advised to rechallenge anyone who developed neutropenia due to clozapine or any other allergic type of drug-induced agranulocytosis.\textsuperscript{10} Dunk et al\textsuperscript{14} demonstrated how difficult it is to identify with any certainty patients whose blood dyscrasias are unrelated to clozapine and the need for extreme vigilance when rechallenging any patients. As Whiskey and Taylor\textsuperscript{9} pointed out, all decisions to...
restarted clozapine should involve consultation with the manufacturer, referral to a hematologist specialist, where necessary, and thorough education of the patient to the warning signs and symptoms of blood dyscrasias. Kim et al.8 suggested that re-challenging clozapine can be done safely in some cases of very-early-onset schizophrenia with careful monitoring.

We decided to treat with clozapine without using drugs such as granulocyte colony-stimulating factor or lithium, as has been previously suggested.9 Lithium treatment results in neutropenia, increased platelets, and increased circulating CD34+ hematopoietic stem cells. In this case, previous treatment with lithium prescribed for mood symptoms did not change the baseline neutrophil counts. Clozapine allowed the patient to rehabilitate with a good hematologic tolerance (neutrophils >2000/µL) at 1 year with time-standard blood tests, despite an initial hematologic vulnerability.

AUTHOR DISCLOSURE INFORMATION

There were no sources of financial and material support received for this study. This study had no previous presentation. The authors have no disclaimer statements and no conflicts of interest to declare.

Laure Ragonnet, MD
Pascale Abadie, MD
Department of Psychiatry
Centre Hospitalier Universitaire de Caen
Caen, France

Sonia Dollfus, MD, PhD
Department of Psychiatry
Centre Hospitalier Universitaire de Caen
Caen, France and UMR 6232 CNRS CEA Université de Caen
Université Paris Rén Descartes Caen, France
dollfus-s@chu-caen.fr

REFERENCES


Akathisia Associated With Mianserin

To the Editors:

Mianserin, structurally a tetracyclic antidepressant, is a 5-hydroxytryptamine (5-HT)2A receptor antagonist and an α2- and α1-adrenoceptor antagonist. It is commonly used for the management of depression and anxiety disorders. In low doses of up to 15 mg/d, it has been reported to have a therapeutic effect for the management of various drug-induced akathisia.1–5 Akathisia is defined as subjective complaints of restlessness accompanied by observed movements such as fidgeting of the legs, rocking from foot to foot, pacing, or inability to sit or stand still. It is commonly associated with the use of antipsychotic medications but has been reported with antidepressants, calcium channel blockers, and buspirone.6 We wish to report a case of akathisia associated with mianserin in a depressed patient.

CASE REPORT

A 50-year-old man presented to us with a history suggestive of depressive episode for the last 3 months. The symptoms started after he had a financial loss in his business. An examination of his mental status at the time of presentation revealed psychomotor retardation, ideas of helplessness, worthlessness, and hopelessness. He also reported suicidal ideations on and off. His history revealed a similar episode approximately 10 years back, which was treated with imipramine at 150 mg/d. The patient left the treatment after approximately 6 months. His personal and family histories were nonsignificant. A diagnosis of recurrent depressive disorder without psychotic symptoms, with the current episode being severe, was made according to International Classification of Diseases 10th Revision. The patient was started on mianserin at 10 mg/d, which was increased to 30 mg/d on the fourth day. On the fifth day, the patient reported a severe intense motor restlessness and an inability to sit still. The patient was brought to us. He reported inner restlessness and was constantly moving his legs. He was given 1 mg of clonazepam, and his symptoms settled down in approximately 1 hour. The next day, the patient remained calm for the whole day but again reported similar complaints approximately 4 hours after taking the dose. He was immediately brought to us again. This time, a possibility of drug-induced akathisia was considered. Then, his total Barnes akathisia score was 10. Results of neurological examinations including fundus examination, routine blood examinations, and magnetic resonance imaging of the brain were normal. He did not report any psychotic features or any suicidal ideations. Mianserin was stopped and replaced with milnacipran at 25 mg/d, which was increased to 100 mg/d. He was also started on clonazepam at 0.5 mg/d. Clonazepam was stopped after 1 week, and milnacipran was continued. The patient showed improvement in his symptoms, with no recurrence of akathisia. He is currently maintaining well approximately 8 months after starting on milnacipran.
DISCUSSION
The use of the Naranjo adverse drug scale shows a probable relationship with the drug. We could not find any other report of akathisia secondary to mianserin, although reports of akathisia secondary to mirtazapine (an antidepressant with a similar mechanism of action) have been reported. We found reports of restless leg syndrome associated with mianserin, but there were no associated sleep disturbances, violent myoclonic jerks in waking, paresthesias, or night time worsening characteristic of restless leg syndrome reported by our patient. Our patient reported inner restlessness characteristic of akathisia. Our patient developed akathisia after taking a relatively lower dose (30 mg) of mianserin, considering its dose to be up to 90 mg/d. The underlying neurobiological causation of the development of akathisia secondary to the drugs is not clear. It is seen with a variety of drugs with different mechanisms of action. The role of noradrenergic and serotonergic neurotransmitters has been postulated in the pathophysiological characteristics of akathisia. Blockade of α2-adrenoreceptors by mianserin may have a role in the causation of akathisia. One must be vigilant for this adverse effect, especially in patients with elderly depressive disorder, as akathisia itself can lead to suicidal attempts, especially in a patient with depression harboring suicidal ideations.

AUTHOR DISCLOSURE INFORMATION
The authors have no conflicts of interest to declare.

Ashish Aggarwal, MD
Department of Psychiatry
Indira Gandhi Medical College
Shimla, India
drashish1980@gmail.com

Ashish Khandelwal, MBBS
Amit Garg, MD
Ram C. Jiloha, MD
GB Pant Hospital
New Delhi, India

REFERENCES

Mania Associated With Mefloquine Prophylaxis

To the Editors:
Mefloquine is an antimalarial drug used as a prophylaxis agent in Plasmodium falciparum malaria chloroquine-resistant areas. It was introduced for malaria treatment in 1970s and was first used for prophylaxis in 1985. It has been reported that approximately 14.5 million people have used mefloquine for prophylaxis and only 1.6 million for treatment purposes. Mefloquine causes different adverse effects; among the most frequent are the gastrointestinal ones. Neuropsychiatric effects have also been described, such as dizziness, sleep disturbances, trembling, and vivid dreams. Nevertheless, mefloquine can produce severe neuropsychiatric effects (paranoia, depression, hallucinations, etc), and association to autolytic ideation and suicide events have also been reported. The occurrence of psychiatric symptoms such as anxiety, depression, restlessness, or confusion could be a prodominal sign of severe effects. If neuropsychiatric effects appear, mefloquine must be stopped. Mefloquine must be used with caution in patients with a previous history of depression and is contraindicated in patients with an active or recent history of generalized anxiety disorder, depression, or psychotic disorder. In this article, the case of a patient who presented a manic episode with mood-congruent psychotic symptoms during mefloquine prophylaxis is described.

CASE REPORT
Mrs. X. is a 26-year-old white woman who had been working as a tourist guide in Mali for the last 6 months. The patient had started antimalarial prevention with mefloquine 250 mg/wk since her arrival in Mali. She did not have personal or family psychiatric or neurological history. After 6 months of prophylaxis, the patient suddenly developed excessive happiness, incapacity to sleep, and megalomania (she believed to have “special powers and to be the mother of all children”). The patient was admitted to a local hospital for 7 days and received treatment with haloperidol and chlorpromazine (unknown doses). Then, the patient was repatriated to Spain without antipsychotic treatment. After her arrival in Spain, the patient continued with mefloquine prophylaxis, and she continued experiencing the aforementioned symptoms. Fifteen days after arrival, the patient went to the emergency room of our hospital where the psychiatrist on duty proposed admission. Mefloquine was suppressed. Treatment was started with risperidone and clonazepam. At admission, the Clinical Global Impression–Severity of Illness score was 5. Young Mania Rating Scale was 25 points. After 7 days of treatment, the patient had a quick symptomatic improvement; Clinical Global Impression–Severity of Illness and Young Mania Rating Scale scores decreased to 2 and 5 points, respectively. Physical examination and complementary tests were normal. Diagnosis was oriented as a manic episode with mood-congruent psychotic symptoms secondary to mefloquine. The patient was discharged after 15 days under risperidone 6 mg/d and clonazepam 1.5 mg/d. At the 6-month follow-up visit, the patient was clinically asymptomatic and was taking no treatment.

DISCUSSION
Mefloquine has an elimination half-life from 14 to 41 days, allowing a once-a-week dosage of 250 mg. Because of this,
subtherapeutic concentrations can persist in the body for several months. The precise mechanism of action is unknown. The adverse neuropsychiatric effects have been divided into 2 classes: type 1 effects, consisting of mild effects such as dizziness, dysphoria, light-headedness, and concentration problems occurring within 6 hours after intake and usually resolving quickly in the following days; and type 2 effects, including severe neuropsychiatric disorders such as acute psychosis, agitation, or depression. Nevertheless, the most common effects are dizziness, insomnia, and vivid dreams. The incidence of neuropsychiatric effects is lower when prophylactic dosage is used (0.008%–0.7%), and when used at the therapeutic dosage, the incidence in adults reaches up to 14% (0.7% in children). In the same way, the average duration of adverse effects in patients who received mefloquine as treatment seems to be shorter than in those receiving it as prophylaxis (4 vs 16 days).

Risk factors associated with the appearance of adverse effects are history of seizures or psychiatric disorders, female sex, and low body mass index. Alcohol intake and the association with other antimarial drugs, such as quinine, are other risk factors for developing adverse effects.

Another factor that is related to adverse effects is the MDR1 gene polymorphism. P-glycoprotein is a product of the multidrug resistance 1 gene (MDR1/ABCB1) located on chromosome 7p21 and plays a role in the uptake and distribution of mefloquine. P-glycoprotein is an efflux pump and is expressed in the intestine and in the blood-brain barrier. Mefloquine is a substrate for P-glycoprotein, but it is also an inhibitor of its function. A prospective study in 89 white travelers taking mefloquine prophylaxis revealed that the ABCB1 1236TT/2677TT/3435TT haplotype was associated with a high risk of neuropsychiatric symptoms (more frequently in women). Individuals carrying ABCB1 T variants may have a lower mefloquine efflux from the brain, exposing them to high tissue concentrations related to neuropsychiatric symptoms. This finding might suggest the important role of local MDR1 expression at the blood-brain barrier that leads to the accumulation of mefloquine without affecting systemic exposure.

Other mechanisms that may explain melfloquine neurotoxicity would be the interference with neuronal calcium ion homeostasis, adenosine 2A receptor blockade (because adenosine is important in sleepiness promotion and mefloquine is an antagonist, therefore declining sleeping necessity), acetyl cholinesterase and butyryl cholinesterase inhibition, and enhancement of striate γ-aminobutyric acid.

The World Health Organization recommends that travelers with a personal or family history of seizures or bipoliar disorder should not take mefloquine prophylaxis. However, the Centers for Disease Control in the United States and the Committee to Advise on Tropical Medicine and Travel in Canada do not recognize these as contraindications to take mefloquine. Moreover, the Centers for Disease Control indicates drugs such as atovaquone/proguanil, doxycycline, or primaquine when mefloquine is suppressed, in case of psychotic or manic symptoms, treatment with atypical antipsychotics such as risperidone or quetiapine has demonstrated being effective, with symptomatic remission within a few days.

Finally, we may conclude that it is important to consider the possibility that mefloquine may produce adverse effects and should only be prescribed following the World Health Organization recommendations.

**AUTHOR DISCLOSURE INFORMATION**

None of the authors reported biomedical, financial, or potential conflict of interest. No funding for research has been received.

**Silvia Velmo, MD**
Department of Psychiatry
Hospital Universitario de Canarias
Santa Cruz de Tenerife, Spain
silviayelmo@gmail.com

**Armando L. Morera-Fumero, MD, PhD**
Department of Internal Medicine
Dermatology and Psychiatry
Universidad de La Laguna
Santa Cruz de Tenerife, Spain

**Manuel Henry, MD, PhD**
Department of Psychiatry
Hospital Universitario de Canarias
Santa Cruz de Tenerife, Spain

**Alicia Renshaw, MD**

**Ramón Gracia-Marcos, MD, PhD**
Department of Psychiatry
Hospital Universitario de Canarias
Santa Cruz de Tenerife, Spain

**REFERENCES**

Low Serotonergic Function and Its Normalization by Treatment With Sertraline in Obsessive-Compulsive Disorder—An Auditory Evoked Potential Study

To the Editors:

Obsessive-compulsive disorder (OCD) affects approximately 2% to 3% of the general population. Disturbed frontocortical-subcortical neuroanatomical pathways as well as biochemical abnormalities of central serotonergic functioning are important factors in the pathophysiology of the disease. In particular, treatment with selective serotonin reuptake inhibitors (SSRIs), 5-HT transporter abnormalities, increased concentrations in cerebrospinal fluid of the primary metabolite of serotonin (5-HIAA) are suggestive for the involvement of the serotonergic system in the disease. To overcome previous methodological limitations, we assessed the loudness dependence of auditory evoked potentials (LDAEP). The method is considered to be a valid indicator of the synaptically released serotonin. 2-10 Intensity dependence of sensory evoked potentials denotes the increase or decrease of the amplitude of a late component because of the increase of stimulus intensity, for example, loudness. There is strong evidence indicating that the LDAEP of the primary auditory cortex is closely related to the central serotonergic function in an inverse manner: a strong LDAEP of the primary auditory cortex is related to low serotonergic activity, and vice versa. 11-13 The aim of the present study was to investigate whether patients with OCD are characterized by a stronger loudness dependence of the primary (AEP N1/P2-component, tangential dipole) but not of the secondary auditory cortex (radial dipole), indicating reduced serotonergic function, as compared with healthy controls. Additionally, it was investigated whether the LDAEP of the primary auditory cortex decreased after a 10-week treatment with the SSRI sertraline.

Forty-eight inpatients (28 male and 20 female subjects, 32.1 ± 10.0 years old) from the Psychosomatic Clinic Windach, who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for OCD and reached a score of 18 or higher on the Yale-Brown Obsession-Compulsion Scale (Y-BOCS)11 were included in the study. Exclusion criteria for patients were concurrent psychiatric, neurological, or somatic illnesses. Patients were free of medication for at least 2 weeks. After baseline LDAEP recording and psychopathological ratings (Y-BOCS, 25.1 ± 4.3), Hamilton Depression Rating Scale (13.6 ± 6.3), 12 Maudslay Obsessive-Compulsive Inventory (13.3 ± 4.4), 13 Beck Depression Inventory (17.7 ± 9.1), 14 Clinical Global Impression (5.6 ± 0.6), patients were treated with sertraline for a period of 10 weeks (73% of the patients received 50 mg/d; in 27% of the patients, sertraline was increased to 100 mg/d). Recordings of 31 patients were suitable to be analyzed before and after treatment with sertraline. Patients were compared with 48 completely healthy matched volunteers (20 male and 28 female subjects; 34.3 ± 12.3 years old) recruited from the local population, using a random list from the local registration office. They had no first-degree relative with a psychiatric disorder.

All participants investigated gave their informed consent. The study was approved by the local ethics committee and was carried out in accordance with the Declaration of Helsinki.

Evoked responses were recorded with 33 electrodes referred to Cz (32 channels) according to the 10/20 system, and with an electrooculogram electrode placed laterally from the corner of the left eye (SynAmps, Neuroscan, El Paso, Tex). Sinus tones (1000 Hz, 40 milliseconds’ duration time, inter stimulus interval randomized between 1800 and 2200 milliseconds) of 5 intensities (60, 70, 80, 90, and 100 dB sound pressure level) were binurally presented in a pseudo-randomized form via headphones. Data were collected with a sampling rate of 256 Hz and an analogous band-pass filter (0.16–70 Hz). Two hundred–millisecond prestimulus and 600 poststimulus periods were evaluated for 100 sweeps of each intensity (all together, 500 sweeps). Dipole source analysis was performed using brain electrical source analysis. 7,12 The LDAEP was measured for the tangential and radial dipole activity using the median slope technique.

Group differences were assessed by the 2-tailed t test or nonparametrically by the Mann-Whitney U test in case of small sample size. Longitudinal data were analyzed by paired t tests with dependent groups. Pearson and Spearman correlation coefficients were calculated for intrindividual relationships. Analysis of covariance was used for covariance analysis, and multivariate analysis of covariance was used for analyses of interaction effects and repeated measurement effects.

There was a significant negative correlation between age and LDAEP of the tangential dipole in patients with OCD (r = −0.30, P = 0.04). Medication-free patients with OCD were characterized by a significantly stronger LDAEP of the tangential dipole compared with healthy controls (t test: P = 0.006). This difference remained when age (F1,64 = 13.9, P < 0.001), years of education (F1,64 = 6.3, P = 0.01), Y-BOCS (F1,64 = 4.8, P = 0.01), or sex (F1,64 = 8.3, P = 0.005) were used as covariates. Patients with an onset of the disease with less than 17.5 years (n = 23) revealed a higher difference of the LDAEP of the tangential dipole, compared with healthy controls (0.31 ± 0.25 vs 0.17 ± 0.14 μV/10 dB, P = 0.002), than patients with an onset of the disease later than 17.5 years (n = 25) (0.24 ± 0.19 vs 0.17 ± 0.14 μV/10 dB, P = 0.08). No difference between OCD patients and healthy subjects was found for the LDAEP of the radial dipole. The LDAEP of the tangential dipole was analyzed in patients and controls (14 female and 17 male subjects each, 33.5 ± 10.4 vs 37.0 ± 13.0 years old) after 10 weeks of treatment. The OCD symptoms significantly improved as measured via Y-BOCS (25.3 ± 4.3 to 13.7 ± 7.0; P < 0.001). Furthermore, after sertraline, a decreased LDAEP of the tangential dipole (0.27 ± 0.24 vs 0.22 ± 0.20 μV/10 dB, P = 0.08, statistical tendency) was observed in patients (Fig. 1). This reduction reached full statistical significance regarding the LDAEP of the tangential dipole for the right hemisphere (0.30 ± 0.28 vs 0.15 ± 0.24 μV/10 dB, P = 0.01). Only OCD patients with an onset of the disease later than 17.5 years (n = 18) revealed significant reduction of the LDAEP (0.23 ± 0.21 vs 0.15 ± 0.16 μV/10 dB, P = 0.02) but not those with an onset of the disease less than 17.5 years (0.33 ± 0.27 vs 0.32 ± 0.22 μV/10 dB, not significant).

The LDAEP of primary auditory cortex was found to be stronger in medication-free patients with OCD in comparison to healthy subjects. Thus, we suggest that OCD is characterized by a serotonergic deficit underlying results of a previous neuroimaging study. Furthermore, the LDAEP of the tangential dipole became weaker compared with baseline

© 2010 Lippincott Williams & Wilkins www.psychopharmacology.com | 341
values after sertraline treatment, indicating an increase of serotonergic activity. Although the sertraline treatment was not controlled in a close sense, and the influence of nonrelated factors cannot completely be excluded, this result can be explained in a strong biological way but not as a pure clinical aftereffect because it was not related to corresponding changes of the psychopathological state. Our results are at variance to a previous pilot study revealing no difference between LDAEP of tangential dipole between OCD patients and healthy controls. Patients of the present study were severely ill and unmedicated. In contrary, patients of the pilot study were already treated psychotherapeutically. Previous data suggest that behavioral therapy impacts central biological and biochemical parameters in patients with OCD. The treatment with sertraline over an observation period of 10 weeks led to both a significant clinical improvement and a significant reduction in LDAEP, which might suggest a normalization of serotonergic function. However, there was no correlation between the individual changes of disease severity and the respective changes in the LDAEP, suggesting a direct impact of sertraline on the LDAEP independent of disease severity. Interestingly, there was a difference of LDAEP between patients with early onset and late onset. Patients with an onset of the disease less than 17.5 years revealed a higher difference of the LDAEP when compared with the controls. This difference suggests a stronger serotonin deficit in the early onset OCD subgroup. However, it is not clear why a treatment with SSRI in this subgroup did not lead to a significant reduction of LDAEP as observed in the late onset OCD subgroup. This discrepancy could be due to differences in the pathophysiology of the disease in both groups.

ACKNOWLEDGMENTS
This study was partly supported by an unrestricted grant from the Pfizer Pharma, Germany. The statistical analyses were performed by Dr Juckel.

REFERENCES

Christoph Mulert, MD, PhD
Department of Psychiatry
Ludwig Maximilians University Munich, Germany

Michael Zaudig, MD, PhD
Psychosomatic Hospital Windach, Germany

Ulrich Hegerl, MD, PhD
Department of Psychiatry
Ludwig Maximilians University Munich, Germany

Georg Juckel, MD, PhD
Department of Psychiatry
Ludwig Maximilians University Munich, Germany

Paraskevi Mavorgiorgou, MD
Department of Psychiatry
Ludwig Maximilians University Munich, Germany

DOI: 10.1038/jcp.2010.26

© 2010 Lippincott Williams & Wilkins


Several hypotheses exist about the etiology of depression, including the monoamine hypothesis, the stress hypothesis and, in the case of late-life depression, the vascular hypothesis. Most antidepressive treatments are based on the monoamine hypothesis and, recently, also on the stress hypothesis. In the last 20 years, a growing amount of evidence has emerged supporting yet another, inflammatory hypothesis. This hypothesis states that immune activation with abnormal cytokine levels may have reciprocal influences on the central nervous system and contribute to the pathophysiology of depression. In animal studies, injection of cytokines cause behavioral changes (sickness behavior), which resemble depressive symptoms in humans. Cytokine treatment of certain tumors and chronic hepatitis in humans can cause depressive symptoms, and depression often accompanies chronic noninfectious autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and allergy. In addition, immune activation has been associated with clinical depression, and several antidepressive treatments affect immune parameters. Furthermore, the aging process may play a vital role in causing immune system dysregulation, eg, chronic low-grade hyperactivation, and, concordant with the supposed etiology of dementia, the inflammatory hypothesis might thus be particularly true in late-onset depression.

To our knowledge, to date, no antidepressive treatment has been targeted at immune activation. In the treatment of autoimmune diseases such as psoriasis, chronic rheumatoid arthritis, tumor necrosis factor alpha (TNF-α) antagonists are being used to reduce inflammation. Remarkably, administration of TNF-α antagonist etanercept in psoriasis was associated with increased well-being and decreased depressive symptoms independent of the improvement of psoriasis. Therefore, we aimed to investigate the effectiveness of TNF-α antagonist infliximab for late-onset depressive disorders, in the absence of a prominent autoimmune disease. We set up a randomized placebo-controlled trial (ISRCTN65900535) in which patients 60 years and older with a late-onset (>55 years) antidepressant-resistant depressive disorder (dysthymia, minor depression, or major depression according to the Standardized Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [SCID]) were randomized to either a single 3-mg/kg dose of infliximab intravenously or a placebo. Patients on an MMSE score of less than 22 points, psychotic symptoms, bipolar disorder, severe suicidality, active infectious diseases, (suspicion of) tuberculosis, cardiac failure, prior treatment with recombinant antibodies, or allergy to infliximab were excluded. Severity of depressive symptoms was assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) score at baseline and after 8 weeks of follow-up.

Unfortunately, recruitment and inclusion of patients were so disappointing that the trial had to be stopped prematurely. A total of 24 patients were referred to the study. Ten patients gave informed consent of which 7 patients could be included. The 5 patients who received infliximab are described as a case series in this letter. The first 3 patients were treated in an open-label pilot study and the last 2 were randomized to infliximab infusion. In Table 1, the main demographic, clinical, and outcome characteristics of the 5 study participants who received infliximab are shown. In one patient receiving infliximab in an open-label manner, the depressive symptoms disappeared completely, and remission lasted for at least 16 weeks. Although this antidepressive effect was extraordinary, it could have been a placebo response because her treatment had not been blinded. This particular patient had psoriasis, an autoimmune disease. Earlier, a positive effect of etanercept, another TNF-α antagonist, was shown on depressive symptoms in patients with psoriasis. In one patient randomized to infliximab treatment, a substantial decrease of depression severity was seen (44% decrease in MADRS score) within 4 weeks of follow-up, but unfortunately, this improvement was not felt by the patient himself. Regular antidepressive drugs were requested before the end of the follow-up phase. In the other 3 patients, no effect of infliximab infusion could be demonstrated. There were no serious adverse events, and the reported adverse effects were mild. One patient in the pilot study developed rectal bleeding and fever, and collapsed 7 weeks after infliximab infusion. However, the safety committee concluded that because of the 7-week time lag and lack of hematological changes during the 2- and 4-week follow-ups, a relation with infliximab was not plausible.

It is possible that the single, rather low dose of 3-mg/kg infliximab that was given in our study was suboptimal, thus failing to demonstrate positive results. In comparison, autoimmune diseases such as psoriasis, chronic disease, and rheumatoid arthritis are being treated with repeated infusions of infliximab in a dose of 5 mg/kg. Furthermore, it remains to be elucidated whether only certain depressions are associated with immune activation. Different depressive disorders may

© 2010 Lippincott Williams & Wilkins

www.psychopharmacology.com
TABLE 1. Demographic, Clinical, and Treatment Characteristics of the Patients Receiving Infliximab 3 mg/kg Intravenously (n = 5)

<table>
<thead>
<tr>
<th></th>
<th>Not Randomized</th>
<th>Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Age, y</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td><strong>Clinical and treatment characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis according to SCID</td>
<td>Major depression</td>
<td>Major depression</td>
</tr>
<tr>
<td>Age of onset, y</td>
<td>56</td>
<td>63</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Somatic diseases</td>
<td>None</td>
<td>COPD</td>
</tr>
<tr>
<td>MADRS score baseline</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>MADRS score after 8 wk</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Medication*</td>
<td>Fluoxetine, sertraline, citoprop, nortriptyline</td>
<td>Paroxetine, venlafaxine</td>
</tr>
<tr>
<td>Possible adverse effects</td>
<td>Dizziness</td>
<td>Light nausea</td>
</tr>
<tr>
<td>Dropout</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Dose was calculated according to the regular treatment protocol used in the Leiden University Medical Center; 3 mg/kg was rounded off to 100 mg owing to ampoule size.

*Medication in sufficient doses used for at least 6 weeks or discontinued because of adverse effects.

Authors have no conflicts of interest. No funding/support was received for this work.

REFERENCES
Metformin Provides Weight Reduction for Hospitalized Patients Receiving Polypharmacy

To the Editors:

The National Diabetes Prevention Program presented research indicating that metformin (MET) is effective in the attenuation of weight gain among overweight/obese patients and that it may decrease the risk of these individuals acquiring type 2 diabetes (T2D).1,2 There is further controlled research indicating MET’s effectiveness either in attenuating weight gain3 or decreasing the weight of both adult patients receiving monotherapy antipsychotic medication (AP)4–5 and adolescent patients on monotherapy AP and stable dose anticonvulsant.5 The mechanism of MET’s action is speculative; however, it apparently decreases insulin resistance, which may be related to both its effect on decreasing weight and its prevention of the metabolic syndrome.5

Although good evidence of weight reduction using MET is provided by 4 random assignment studies,2–5 these studies provided monotherapy for their subjects, leaving unanswered whether MET might be effective in the messy real-life hospital ecological setting where patients routinely receive polypharmacy. Studies have shown that patients receiving polypharmacy are at the highest risk of developing adverse metabolic consequences6 and that chronic patients are most at risk for polypharmacy.9

Thus, a need exists to show the possible effectiveness of MET in the chronic care hospital environment.

Here, we report on a performance improvement project provided for at-risk patients in our facility, a 180-bed intermediate care psychiatric hospital, who agreed to treatment to reduce weight with MET 1500 mg/d (750 mg twice per day) and a supervised program of exercise. We modeled this intervention in keeping with the findings of the National Prevention of Diabetes Study, which showed a beneficial effect of weight reduction and prevention of the metabolic syndrome among subjects separately receiving MET (1700 mg/d) or exercise.1

Sixteen patients with a diagnosis of schizophrenia or schizoaffective disorder who had a body mass index (BMI) of 24 or greater and who gave their consent for participation were enrolled in the performance improvement project. Thirteen patients completed the 16-week project. The 3 noncompleters were lost consequent to intercurrent infection (1), noncompliance (1), and discharge (1). The participants ranged in age from 23 to 59 years (mean age 46.4; SD ±11.6 years), were of both sexes (6 male and 7 female subjects), and with length of stays ranging between 1.2 and 37.8 years (mean stay 16.6; SD ±11.75 years). The group’s mean initial weight was 92.9 kg (range 65.3–126.0 kg; SD, ±5.2). BMI was ranged from 24 to 52.5; mean BMI was 32.2 (SD, ±7.3). The mean initial HbA1c was 5.8 (range 2.3–6.4; SD, ±0.34). Of the 13 patients participating in the MET program, all 13 were on atypical antipsychotics, 7 were on typical antipsychotics, and 6 were on both atypical and typical antipsychotics. Eight patients were on selective serotonin reuptake inhibitors. In addition, of the 13 patients, 9 were receiving antiepileptics for mood stabilization: 5 were on depakote, 1 was on lamictal, and 3 were on antiepileptics other than depakote or lamictal. On average, each patient was receiving 3.7 psychotropic drugs. Patients were prescribed MET 1500 mg/d in an open label, and no placebo was provided in keeping with the clinical management, noneperimental design of the intervention. Patients were treated for a 16-week period. Side effects were monitored clinically, and weight and waist circumference were assessed at baseline, 8, and 16 weeks. Standard clinical laboratory measures were obtained and are available on request. Weight obtained 16 weeks before MET initiation served as a contrast to the weight change measured while on MET. In accordance with the National Diabetes Prevention Study1 procedure, participating patients were offered 150 minutes of exercise per week; however, because of poor compliance, the average patient only participated in 37.1 minutes of exercise per week. Body mass index, weight, and HbA1c data are reported here. No significant adverse effects were noted or reported during the treatment period.

Patient weights were steady before project enrollment, with a nonsignificant 0.14-kg mean weight gain over the 16–week period before project enrollment for the 12 of 13 patients for whom we have pretreatment data (P = 0.84). For the 13 patients who completed 16 weeks of MET therapy, we found a significant weight loss of 2.5 kg (SD, ±2.0; t12 = 4.6, P = 0.001), similar to that found in previous studies with patients receiving monotherapy.4 Significant decreases were also noted in BMI, with a decrease of 0.86 (SD, ±0.78; t12 = 4.0, P = 0.002) and HbA1c, with a decrease of 0.17% (SD, ±0.17; t12 = 3.5, P = 0.005). When the participants were grouped according to relatively high and low levels of exercise, there was no significant difference in weight change between the groups (t11 = −0.926, P = 0.374).

DISCUSSION

The mortality rate among individuals with schizophrenia shows a 25-year gap as compared with the nonafflicted, and perhaps 60% of this gap is accounted for by cardiovascular and pulmonary disease.10 It is well known that weight gain and smoking are significant contributors to cardiovascular and pulmonary disease and, in some measure, remediable by weight loss and lifestyle changes. The possible prophylactic effect of MET on the adverse weight consequences of AP medication is raised by 4 well-designed studies (reviewed above) in which patients received monotherapy. These studies report either weight stabilization1 or losses of between 1.4 and 3.2 kg.3,4 Although monotherapy is an idealized goal of treatment, patients often receive multiple drugs, and studies have shown that the chronicity of illness increases the likelihood that patients will receive more than 1 antipsychotic medication.9 Such is the case among our hospitalized patient sample (average, 3.7 psychotropics per patient participant). This finding is of grave consequence when coupled with the report by Correll and colleagues8 that polypharmacy contributes to the risk of acquiring the metabolic syndrome.

Our findings of weight loss among our sample of at-risk hospitalized patients receiving polypharmacy treated prophylactically with MET is encouraging, and continued monitoring revealed that the reported weight loss has continued at 32 weeks of treatment. The 10-year data from the National Prevention of Diabetes Study1 has shown that even modest weight loss is associated with the delayed onset of T2D. Such findings, if applicable to patients such as ours, would provide a welcome contribution to the prophylaxis of morbidity among this extremely vulnerable group. However, there are additional prevention measures that can be taken to reduce the metabolic impact of AP treatment. The use of less cardiometabolic risky antipsychotic drugs should be encouraged in clinical care, in addition to...
careful routine metabolic monitoring of antipsychotic-exposed patients. Unfortunately, the belief in the relative safety of the newer generation drugs with respect to weight gain and metabolic risk, with the exception of aripiprazole and ziprasidone, is unsupported, and in fact, findings indicate that some older generation drugs may be safer regarding weight toxicity than the new generation mediations. Of great importance is the encouragement of lifestyle practices conducive to wellness, which are exceedingly difficult to implement among the chronically mentally ill. Nevertheless, we conclude that there is reason to be optimistic about the potential use of MET among patients receiving polypharmacy and that it is important to extend research findings from controlled trials with monotherapy to the less-than-ideal real-life clinical environment.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

Bertrand Winsberg, MD
Catherine Yeager, PhD
Brian Hobbs, MA
Ronald Wei, MD
Natarajan Elangovan, MD
Essex County Hospital Center
Institute for Mental Health Policy
Research and Treatment
Cedar Grove, NJ
bwinsberg@health.essexcountynj.org

REFERENCES


Topiramate for Bruxism
Report of 2 Cases

To the Editors:

Bruxism is the jaw clenching or grinding of teeth that usually occurs during sleep. It has recently been classified as a “sleep-related movement disorder.” Sleep bruxism may cause severe harm to the temporomandibular joint, orofacial pain syndrome, muscle contraction headache, excessive tooth wear, or tooth fracture.

In current literature, the relationship between emotional stresses and bruxism has received more attention, whereas the connection of the occlusal interference to bruxism lacks evidence-based data.

Treatment approaches toward bruxism include occlusal interventions and oral splints, behavioral approaches, and pharmacological treatments. A review of literature shows that there are insufficient evidence-based data on which to draw definite conclusions concerning the pharmacological treatment of bruxism. However, certain dopaminergic, serotonergic, GABAergic ( γ-aminobutyric acid [GABA]), and adrenergic medications have been reported to suppress or induce bruxism activity in humans and animals.

Topiramate was first available for the adjunctive treatment of epilepsy in the United States in 1997. The exact mechanism of action of topiramate is unknown. It has been shown to potentiate the activity of GABA, an inhibitory neurotransmitter.

We report 2 patients with bruxism who were successfully treated with topiramate. To our knowledge, these are the first reports of topiramate in the management of bruxism.

CASE REPORTS

The patients were informed about the aims of the study and possible adverse effects of the drug. They gave their consent before being enrolled in the study. The study was approved by the local ethics committee that adheres to the Declaration of Helsinki: Ethical Principles for Medical Research involving human subjects.

Case 1 is a 23-year-old woman who was referred to our clinic because of loud nocturnal grinding for a few months. The patient was experiencing clenching and grinding of her teeth during the night, with sore jaws and teeth, especially on awakening in the mornings. She was urged to visit a doctor by her mother. Topiramate 25 mg at bedtime was started and then increased to 50 mg after 1 week. After that, our patient’s mother reported no more nocturnal noises. She herself was also happy, being relieved from morning facial pains. At follow-up after 1 month, she was not experiencing bruxism any more.

Case 2, a 32-year-old man, was referred to our clinic because of night-grinding noises and morning jaw pain that had begun a few months earlier. His wife reported nocturnal noises that had frequently awakened her. In psychiatry examination, he seemed to experience obsessive-compulsive personality disorder.

Topiramate 100 mg at bedtime reduced the bruxing sounds and orofacial pains substantially. His wife reported no more nocturnal grinding noise. At follow-up, there was no history of bruxism after 3 months.

DISCUSSION

Our experience demonstrates successful management of bruxism with topiramate in 2 patients. This may open a new path in the treatment of bruxism.
Most recent publications indicate that rhythmic microarousals in brain and autonomic nervous system contribute to the increased motor activity underlying the genesis of bruxism. These microarousals tend to be repeated 8 to 14 times per hour of sleep. Medications that suppress these arousals may be effective in controlling bruxism.

Potentiating the GABAergic system, as an inhibitory system, may reduce the brain microarousals underlying bruxism. In line with this hypothesis, some GABAergic medications such as clonazepam, tiagabine, and gabapentin have shown effectiveness in suppressing bruxism.

Topiramate has been shown to potentiate the activity of GABA, an inhibitory neurotransmitter. Increased activity of GABA would be expected to reduce brain arousals and subsequent motor activity and thus might reduce involuntary sleep movements such as bruxism. Topiramate also inhibits the activity of excitatory glutamate via glutamate receptors.

In conclusion, our experience shows that topiramate is effective for the treatment of bruxism. Topiramate, by potentiating the activity of inhibitory GABA in the brain, may reduce bruxism. However, larger double-blind, placebo-controlled studies are needed to confirm our conclusion.

AUTHOR DISCLOSURE INFORMATION
The authors declare no conflicts of interest.

Arash Mowla, MD
Department of Psychiatry
Persian Gulf Bioscience Research Center
Bushehr University of Medical Sciences
Bushehr, Iran
mowlaar@gmail.com

Behrang Sabayan, MS
Department of Psychiatry
Shiraz University of Medical Sciences
Shiraz, Iran

REFERENCES

Modafinil-Associated Vivid Visual Hallucination in a Patient With Kleine-Levin Syndrome

To the Editors:

Kleine-Levin syndrome (KLS) is a rare sleep disorder characterized by recurrent episodes of hypersomnia and accompanied by cognitive and behavioral abnormalities, such as hyperphagia and hypersexuality. Several treatment strategies such as stimulant drugs, antiepileptic drugs, antidepressants, antipsychotic drugs, antivirals, lithium, hydrocortisone, melatonin, benzodiazepines, and levodopa-benserazide have all been used with variable success. After the success of modafinil in the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy, modafinil is also tried to manage hypersomnia related with other neurological disorders such as obstructive sleep apnea/hypopnea syndrome and shift-work sleep disorder.

The application of modafinil in EDS associated with KLS is rare, and we did not find reports regarding modafinil-associated psychosis in KLS. We present our experience of modafinil-associated vivid visual hallucination in a 13-year-old girl with KLS.

CASE REPORT

A 13-year-old girl had been noted to have episodic EDS since she was 11 years old. Up to 7 episodes of EDS were noted in the 2 years. Each episode often happened after an event of upper respiratory tract infection. The duration of EDS ranged from 4 to 9 days, and the interval ranged from 1 to 9 months. Apart from the hypersomnia, she demonstrated derealization and inattention, but she denied any hyperphagia and hypersexuality during the episodes. She was not depressed and had fair to good school performance between attacks. Precordium, short stature (height, 140 cm; weight, 33 kg), and irregular menstrual cycles were noted. She came to our sleep clinic for help. Neurological examination was unremarkable. Laboratory data showed normal complete blood count, liver function, renal function, electrolytes, and thyroid function except a lower cortisol level (2.1 µg/dL at 10 pm) and human growth hormone level (<0.28 ng/mL). Overnight polysomnography showed normal sleep architecture, apnea-hypopnea index, and periodic limb movement index. Multiple sleep latency test showed a mean sleep latency of 9.1 minutes associated with 3 sleep-onset rapid eye movement periods over 5 tests. Kleine-Levin syndrome was diagnosed according to the International Classification of Sleep Disorders, Second Edition diagnostic criteria of KLS.

Methylphenidate was tried in another hospital, but no improvement of EDS was found. She was admitted to our hospital, and modafinil was tried. She took 1 dose of modafinil (200 mg) in the morning (around 7 AM) and went back to sleep. She became awakened around 11 AM, but unfortunately, vivid visual hallucination developed. She saw a lot of skulls floating on the floor of her room. She became agitated and frightened, asking for changing the room. Electroencephalogram on the day of visual hallucination revealed scattered theta waves at 5 to 7 Hz intermixed with posterior 9-Hz alpha activity and intermittent generalized delta activity at 2 to 3 Hz during resting wakefulness, which were compatible with cortical dysfunction. No extra dose of modafinil was given. She had less frequency of visual hallucination, and she
<table>
<thead>
<tr>
<th>No.</th>
<th>Reference</th>
<th>Patient Age, y</th>
<th>Sex</th>
<th>Treated Disease or Symptoms</th>
<th>Other Special Conditions</th>
<th>Combined Medication</th>
<th>Modafinil Dosage When Visual Hallucination Occurred</th>
<th>Onset Time of Visual Hallucination</th>
<th>Duration of Visual Hallucination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yassai-Furukori et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>25</td>
<td>Female</td>
<td>Narcolepsy</td>
<td>Nil</td>
<td>Nil</td>
<td>300 mg/d</td>
<td>6 mo after the initiation of modafinil therapy, 12–24 h after modafinil administration</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>Wu et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>31</td>
<td>Male</td>
<td>Narcolepsy</td>
<td>Surgical excision of a right parietal meningioma; tolerability to modafinil, 400 mg/d for 6 mo without visual hallucination</td>
<td>300 mg of caffeine</td>
<td>At least 500 mg of modafinil</td>
<td>Medication in the morning, and symptoms occurred after lunch</td>
<td>In 1 day</td>
</tr>
<tr>
<td>3</td>
<td>Vorspan et al&lt;sup&gt;9&lt;/sup&gt;</td>
<td>17</td>
<td>Male</td>
<td>Narcolepsy</td>
<td>Tolerability to modafinil, 400 mg/d for 1 y without visual hallucination</td>
<td>Nil</td>
<td>400 mg/d</td>
<td>Full manic episode accompanied by auditory and complex visual hallucination developed within 3 d after reintroduction of modafinil</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>Ivanenko et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Narcolepsy</td>
<td>Another child with a history of visual and auditory hallucinations</td>
<td>Nil</td>
<td>Unknown (200–600 mg daily)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>Oulis et al&lt;sup&gt;4&lt;/sup&gt;</td>
<td>53</td>
<td>Male</td>
<td>Major depression with EDS</td>
<td>Without psychotic symptoms or substance abuse</td>
<td>Venlafaxine, 225 mg/d</td>
<td>200 mg/d</td>
<td>3 wk after initiation of modafinil therapy</td>
<td>Within 1 wk</td>
</tr>
<tr>
<td>6</td>
<td>Freudenreich et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>61</td>
<td>Female</td>
<td>Schizophrenia with EDS</td>
<td>Nil</td>
<td>100 mg of clozapine 3 times daily and 1 mg of lorazepam twice daily</td>
<td>200 mg of modafinil (4 times daily by mouth)</td>
<td>3 wk after initiation of modafinil therapy</td>
<td>Within 2 wk</td>
</tr>
<tr>
<td>7</td>
<td>Mariani and Han&lt;sup&gt;13&lt;/sup&gt;</td>
<td>38</td>
<td>Female</td>
<td>Shift work</td>
<td>Research volunteer, a single oral dose of modafinil (0, 200, or 400 mg) 1 h after waking in 3-d blocks</td>
<td>Nil</td>
<td>400 mg/d</td>
<td>2 d after titration up to modafinil 400 mg/d</td>
<td>In 1 day</td>
</tr>
<tr>
<td>8*</td>
<td>Hsieh et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>13</td>
<td>Female</td>
<td>Kleine-Levine syndrome</td>
<td>Precocity, short stature (height, 140 cm; weight, 33 kg) and irregular menstrual cycles</td>
<td>Nil</td>
<td>200 mg/d</td>
<td>4 h after 1 dose of 200 mg modafinil</td>
<td>8 h</td>
</tr>
</tbody>
</table>

*Our case report.
calmed down in the following couple of hours. She fell asleep around 7 PM, and no further complaint was recorded thereafter. The total duration of psychotic symptoms was around 2.5 hours by estimation. Brain magnetic resonance image on the other days after discontinuing modafinil was normal. Technetium Tc 99m ethyl cysteinate dimer brain perfusion single-photon emission computed tomography showed decreased radioactivity in mesial aspect, inferior portion of both temporal lobes (more prominent at the left side), and slightly in the right occipital lobe.

**DISCUSSION**

The clinical presentation of this patient cannot be explained by any functional psychotic disorder as she lacked other concomitant delusion or thought disorders and her symptoms subsided after withdrawal of modafinil. Although the electroencephalographic findings during the episode of visual hallucination might indicate toxic encephalopathy, the patient did not fulfill the diagnosis of delirium because of preserved orientation and global cognition. Therefore, the most likely diagnosis was modafinil-associated isolated visual hallucination.

Modafinil is a wake-promoting agent approved for the treatment of EDS associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shiftwork sleep disorder. Modafinil is also an adjunctive to antidepressants or antipsychotics to improve psychomotor retardation, fatigue, or negative symptoms in depressive and schizophrenic patients. However, there are limited publications about using modafinil for EDS associated with KLS. Modafinil-related adverse effects such as nausea, headache, insomnia, and nervousness have been described. Modafinil-associated visual hallucination has been reported to occur in adults with narcolepsy receiving high-dose treatment (≥300 mg/d), a child with narcolepsy and previous psychotic symptoms, or patients with psychiatric diseases (schizophrenia or mood disorder) (1) (Table 1). We cannot exclude that the initial dosage of modafinil at 200 mg/d might be too high for this teenaged girl with short stature. As we know, this is the first report of modafinil-associated vivid visual hallucination in patients with KLS.

Dopamine plays an important role in the pathogenesis of psychotic symptoms, including hallucinations. Dextroamphetamine and methylphenidate are known to increase wakefulness by blocking dopamine reuptake, by stimulating dopamine release, or by both mechanisms. Modafinil has replaced dextroamphetamine and methylphenidate as a first-line treatment of EDS in patients with narcolepsy. We do not know the exact mechanism of modafinil, although it is likely to involve some indirect γ-aminobutyric acid inhibition, dopamine receptor agonism, and α₁-adrenergic agonism. Modafinil was found to increase extracellular levels of dopamine in the rat nucleus accumbens, which is innervated primarily by dopaminergic mesolimbic neurons. This enhancing effect of modafinil on the mesolimbic dopaminergic system might account for its hallucinogenic potential. Although modafinil has a good safety profile, we should be aware that it may be associated with vivid visual hallucination in patients with KLS, especially in younger patients with precocity, short stature, and higher initial dosage of modafinil.

**AUTHOR DISCLOSURE INFORMATION**

The authors declare no conflicts of interest.

**Cheng-Fang Hsieh, MD**
Department of Neurology
Kaohsiung Medical University Hospital
Kaohsiung, Taiwan

Department of Neurology
Pingtung Hospital
Department of Health
Executive Yuan
Pingtung, Taiwan

Department of and Master’s Program
in Neurology
School of Medicine
College of Medicine
Kaohsiung Medical University
Kaohsiung, Taiwan

**Chiou-Lian Lai, MD, PhD**
Department of Neurology
Kaohsiung Medical University Hospital
Department of and Master’s Program
in Neurology
School of Medicine
College of Medicine
Kaohsiung Medical University
Kaohsiung, Taiwan

**Sheng-Hsing Lan, MD, MS**
Department of Neurology
Kaohsiung Medical University Hospital
Kaohsiung Medical University
Kaohsiung, Taiwan

**Ching-Kuan Liu, MD, PhD**
Department of Neurology
Kaohsiung Municipal Hsiao-Kang Hospital
Department of and Master’s Program
in Neurology
School of Medicine
College of Medicine
Kaohsiung Medical University
Kaohsiung, Taiwan

**Chung-Yao Hsu, MD, PhD**
Department of Neurology
Kaohsiung Medical University Hospital
Department of and Master’s Program
in Neurology
School of Medicine
College of Medicine
Kaohsiung Medical University
Kaohsiung, Taiwan
cyhsu@kmu.edu.tw

**REFERENCES**


13. Mariani JJ, Hart CL. Psychosis
Electroconvulsive Therapy as a Potentially Effective Treatment for Severe Serotonin Syndrome

Two Case Reports

To the Editors:

Although many fatal cases had been reported due to serotonin syndrome (SS), the treatment of severe SS is not yet established. Electroconvulsive therapy (ECT) has been reported to be effective against neuroleptic malignant syndrome (NMS). Serotonin syndrome is a similar neurotoxic syndrome; however, there are few reports on the efficacy of ECT for SS. We encountered 2 patients with recurrent major depressive disorder (MDD) in whom ECT was effective against severe SS with malignant catatonia (MC) associated with antidepressants. In both cases, the patients’ guardians provided written informed consent for ECT. Atropine sulfate, propofol (1 mg/kg), and succinylcholine (0.8 mg/kg) were used for ECT. Stimulus levels for the ECT were determined by the half-age method, and brief-pulse square wave was delivered using Thymatron System IV (Somatics Inc, Lake Bluff, Ill).

CASE 1

The patient was a 67-year-old man. He was diagnosed with MDD at the age of 51 years. He had experienced 2 recurrences of MDD subsequently and had been treated with mianserin (30 mg/d), amitriptyline (75 mg/d), amoxapine (75 mg/d), clomipramine (75 mg/d), and paroxetine (20 mg/d), separately. But he had developed paroxysmal hot flushes and sweating while taking these antidepressants, except with mianserin.

In October 2006, he had a relapse of MDD and visited our hospital on November 11, 2006, and the administration of paroxetine (20 mg/d) was resumed. On November 30, while the depressive symptoms persisted, transient hyperthermia for 3 hours each day developed. He developed a transient obsessive idea that “I am afraid of being urged to kill people” and also developed hot flushes and marked sweating on December 2. He manifested tremors and muscle rigidity with hyperthermia several times a day. From December 10, he had occasional disorientation. He exhibited psychomotor slowing and needed assistance in walking.

On December 13, he was brought to our emergency department and was immediately hospitalized. Physical examination revealed labile consciousness, pyrexia (37.9°C), elevated blood pressure (153/100 mm Hg), and tachycardia (100 beats/min). The pupils were rather dilated. Marked hot flushes, sweating and pyrexia, and tremors of the fingers were observed. Myoclonus was noted in the face and limbs. Tendon reflexes were generally exaggerated. Paroxysmal episodes of aggravation of generalized muscle rigidity, tremors, and marked myoclonus lasting for several hours were frequently observed, which led to rapid breathing and tachycardia (180 beats/min). He had catatonic syndrome with akinetic mutism and catalepsy and periodically exhibited a stuporous state and confusional state with disorientation. Occasionally, he nodded slightly in response to questions; however, communication was difficult, and sometimes visual hallucinations and delusions were noted. Laboratory examination revealed slight leukocytosis (10.14 ¥ 10³/µL) and slight elevation of the serum alanine transaminase (48 U/L) and blood urea nitrogen (28.9 mg/dL). The serum levels of thyroid hormones and electrolytes were within reference range. Electroencephalography revealed no abnormality, and the basic rhythm was dominated by β-waves. Brain magnetic resonance imaging revealed no abnormality. His limbs and body were restrained, and parenteral nutrition became necessary. Based on the suspicion of SS, paroxetine was decreased on admission and discontinued on the day after the admission.

The score on the SS scale (SSS) was 15. During the confusional state, the generalized muscle rigidity, pyrexia, sweating, tremors, and rapid breathing became even more aggravated, and dyspnea due to muscle rigidity was associated with a low level of oxygen and significant sinus tachycardia, which necessitated daily intravenous administration of diazepam. The benefit of diazepam persists for approximately 20 minutes. The psychiatric symptoms dramatically fluctuated. From 3 days after the admission, he had diarrhea (>10 times a day). The pyrexia was aggravated, and at 5 days after admission, the body temperature reached 38.4°C. But no evidence of complicating infections was detected. Paroxysmal muscle rigidity and myoclonus and the confusional state also gradually worsened. Despite discontinuation of the causal drug, paroxetine, the SSS score eventually increased to 23. Six days after admission, cerebrospinal fluid (CSF) examination was performed to exclude encephalitis, and it revealed no inflammation. Cerebrospinal fluid levels of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) were measured (34.5 and 7.6 ng/mL, respectively), and blood examination revealed increase in the blood levels of the catecholamines, 5-HIAA, and HVA. Administration of paroxetine was discontinued, and dehydration was corrected; however, no symptomatic improvement was obtained. The poor nutritional status due to severe autonomic and neurological symptoms rapidly progressed.

Seven days after admission, ECT was administered. After the first ECT, marked improvement of the sweating and paroxysmal tachycardia was noted. His muscle rigidity, myoclonus, and tremors disappeared completely, and the autonomic nervous symptoms were also scarcely observed. After the third ECT, the agitation also abated, with disappearance also of the autonomic nervous symptoms such as pyrexia and diarrhea. He became alert and clear completely, and oral intake was resumed. After the fifth ECT, a second CSF examination showed increased levels of HVA and 5-HIAA (53.8 and 28.0 ng/mL, respectively). The 3-methoxy-4-hydroxyphenylglycol level in the CSF was not changed (11.9 ng/mL before vs 10.5 ng/mL after the ECT). The blood levels of the catecholamines, 5-HIAA, and HVA also tended to be restored. Ten sessions of ECT were performed for sustained remission of MDD. The time course of changes on total SSS score in response to the ECT sessions is summarized in Figure 1. Administration of milnacipran was started, with the dose slowly increased up to 100 mg/d. He was finally discharged on January 2007. Until December 2009, he has shown no relapse.

CASE 2

The patient was a 66-year-old man. He was diagnosed with MDD at the age of 44 years. He experienced a recurrence of MDD and was treated with sulpiride (300 mg/d). In March 2007, he developed depressive mood, hypohelia, insomnia, palpitations, and difficulty in swallowing. Several examinations in an internal medicine clinic revealed no abnormality, and
he was referred to a psychiatric clinic. Sulpiride (150 mg/d) was prescribed, with no effect. He lost 9 kg over 2 months because of loss of appetite. Paroxetine (20 mg/d) was added to the treatment, with no effect. He was referred to our hospital on June 2007. He was diagnosed with MDD and was hospitalized. A high level of anxiety, agitation, depressive mood, hypobulia, loss of appetite, and insomnia were noted. His vital signs were normal.

We discontinued sulpiride and instead increased the dose of paroxetine to 40 mg/d, with no effect. We planned to switch the medication from paroxetine to clomipramine and started clomipramine in combination with paroxetine on July 24. The dose of clomipramine was gradually increased and reached 150 mg/d on August 8; however, transient hyperpyrexia and tremors of the fingers appeared on August 10. Thus, the dose of clomipramine was decreased and discontinued on August 12, but he developed pyrexia (37.8°C), sweating, tachycardia (120 beats/min), elevated blood pressure (156/106 mm Hg), hot flashes, generalized muscle rigidity, tremors (especially of the fingers), and myoclonus of the face. The tendon reflexes were generally exaggerated. Auditory and visual hallucinations and delusions appeared. With marked agitation and excitement, he suddenly made an attempt at suicide saying, “Please let me die,” and tried to escape from the isolation room. He presented labile consciousness disturbance. The blood test results revealed no abnormalities, except for slight anemia (hemoglobin, 12.8 g/dL) and slight elevation of C-reactive protein (0.6 mg/dL); the thyroid hormones and electrolytes were also normal. Brain magnetic resonance imaging and electroencephalography revealed no abnormality.

Based on the dramatic appearance of the psychiatric symptoms, autonomic nervous symptoms, and neurological symptoms, we made the diagnosis of SS. The SSS score was 16. All the drugs were discontinued. On August 14, he had developed marked generalized muscle rigidity and sweating. Because the muscle rigidity was so intense, he bit his tongue, necessitating the use of a mouth gag. The muscle rigidity was alleviated by intravenous administration of diazepam (17.5 mg/d), but once the effect wore off, muscle rigidity with remarkable autonomic nervous symptoms appeared again. Therefore, he was administered a continuous drip infusion of midazolam (10 mg/h). Despite the patient being under continuous sedation, frequently he exhibited generalized muscle rigidity and myoclonus lasting for several hours, which led to reduction of the oxygen level, sinus tachycardia, and hypertension. He repeatedly manifested the following psychiatric states: depressive state with intense anxiety and suicidal idea, transient hypomanic state, stupor with no spontaneous behavior, and confusional state with disorientation. The SSS score was 20, indicating aggravation.

On August 16, ECT was started. After the first ECT, stupor was palliated. Sweating and tachycardia improved. Muscle rigidity and myoclonus disappeared. After the second ECT, although the depressive symptoms and hallucinations/delusions still persisted, he could follow instructions. The autonomic nervous symptoms disappeared. After the third ECT, he could consume all his food. After the fifth ECT, the depressive symptoms were remitted. The time course of changes on total SSS score in response to the ECT sessions in Case 2 is summarized in Figure 1. Thereafter, the administration of sertraline was started, slowly increasing the dose up to 50 mg/d. He was discharged on October 2007. Until December 2009, he has shown no relapse.

### DISCUSSION

Both cases exhibited various psychiatric symptoms, in addition to manifesting diverse neurological and autonomic symptoms. Serotonin syndrome is sometimes viewed as MC, and both cases presented also MC with SS induced by antidepressant.

Our Cases 1 and 2 fulfilled criteria 9 and 7 of SS, respectively, of the 10 criteria proposed by Sternbach, and both cases fulfilled all the 9 major criteria of the modified criteria proposed by Radomski et al; therefore, we considered SS as being a valid diagnosis. Although both cases did not exhibit elevation of serum creatine phosphokinase, they satisfied the criteria for NMS proposed by Levenson. Nonconvulsive status epilepticus and delirium were ruled out based on the electroencephalographic findings.

In Case 1, the responsible drug for SS with MC was considered to be paroxetine. The patient developed nervous hyperpersensitivity, aggravation of anxiety, and transient hyperpyrexia after the start of paroxetine, which suggests that he had developed very mild SS. Typically, SS has been reported to develop within 24 hours of the start of administration or increasing the dose of antidepressants. However, in this case, dehydration was caused by reduced intake of food and fluids, which may result in elevation of the serum level of paroxetine and induces severe SS with MC.

In Case 2, SS with MC may be caused by the enhancement of the serotonergic activity due to the combination of clomipramine and paroxetine as well as by the elevated concentrations of both drugs due to the competitive inhibition of CYP2D6. In neither case did the patient take health foods such as tryptophan or St John’s wort. Serotonin syndrome is considered to be ameliorated in approximately 70% of the cases within 24 hours of discontinuation of the responsible drug, although some cases with protracted symptoms are known. Both cases presented such protracted SS with MC.

It is known that, in some severe or protracted SS, the patient could die of disseminated intravascular coagulation, renal impairment, acidosis, acute respiratory distress syndrome, convulsive seizures, ventricular tachycardia, and so on; 23 fatal cases had been reported by 1999, but the treatment of severe SS is not yet established. Efficacy has been demonstrated against NMS, and some researchers indicate that ECT should be
Electroconvulsive therapy might be also effective for the treatment of SS with MC, which is similar to neurotoxic syndrome. But to date, there are only 2 reports of ECT for the treatment of SS. In a case report, ECT was effective in treating a patient in whom the differential diagnosis between NMS and SS was difficult, and in the other, protracted SS was improved by 4 sessions of ECT. Therefore, involuntary application of ECT for patients with SS, without discontinuation of the causal drugs, should be avoided.

The mechanism underlying the effect of ECT is still unknown. In Case 1, elevated blood levels of catecholamines, except for adrenaline, and HVA and 5-HIAA were observed before ECT, and elevated blood concentrations of noradrenaline, dopamine, and serotonin were suggested, but these abnormalities had improved after remission. Moreover, in the CSF, the levels of HVA and 5-HIAA were increased after remission. In the previous 4 cases of SS reported, it has been observed that the 5-HIAA and HVA levels in the CSF decreased during the active phase of SS. Possibly at the acme of SS, excessive inhibition of presynaptic serotonin reuptake occurs because of the serotonin reuptake effect of the drug, with increase in the serotonin level at the synaptic gap. However, because the presynaptic serotonin level is decreased, the amount of serotonin degraded by monoamine oxidase might also decrease, resulting in a reduction of the 5-HIAA level in the cerebrospinal fluid. Electroconvulsive therapy might correct this excessive inhibition of serotonin reuptake.

REFERENCES

Comments on “Delayed Loss of Efficacy and Depressogenic Action of Antidepressants”

To the Editors: In response to the article Delayed Loss of Efficacy and Depressogenic Action of Antidepressants by Raja,1 the author brought to light the important phenomena of treatment resistance to antidepressants and the emergence of dysphoria with chronic antidepressant use. However, the one important cause of treatment resistance that was not addressed was the issue of missed bipolar disorder. In a population of patients who were initially referred for treatment of refractory unipolar depression, Sharma et al2 found that 80% showed evidence of a bipolar diathesis at 1-year follow-up. Additional studies by Rybakowski et al3 and Calabrese et al4 have also served to show a high prevalence of underlying bipolarity in samples of patients with treatment-resistant unipolar depression. The phenomenon of antidepressant-associated chronic irritable dysphoria reported by El-Mallakh and Karipot5 was initially described in patients with a diagnosis of bipolar disorder after exposure to antidepressants for treatment of bipolar disorder. As noted in the article, antidepressant-associated chronic irritable dysphoria has features of both major depression and hypomania, without meeting the full criteria for a mixed episode. It was hypothesized by El-Mallakh and Karipot that this could represent accelerated rapid cycling. It is conceivable that if mood episodes are fluctuating rapidly, the clinical picture could resemble a mixed state.

In the article, Raja included the treatment initiated after antidepressant withdrawal for each case and the outcome. It is interesting to note that all of the patients ended up on lithium, with some on additional mood stabilizers. All of these patients were reported to have experienced a partial or full remission with discontinuation of antidepressant and subsequent treatment with one or more mood stabilizers. It would be interesting to note on follow-up how many of these patients have underlying
bipolar disorder or demonstrate subsyndromal features of hypomanic or mixed states. The findings in this case series are similar to those found by Sharma in a case series of 15 patients who experienced a loss of response to antidepressants before developing a severe, treatment-resistant depression. All of these patients also exhibited a sustained response to mood stabilizers supporting the hypothesis that many refractory cases of unipolar depression are actually cases of missed bipolar disorder.

**AUTHOR DISCLOSURE INFORMATION**

The authors declare no conflicts of interest. The authors have no sources of support to report.

**REFERENCES**


**Reply to Comments by Drs Shapiro and Verma Posttreatment, Refractory Depression**

To the Editors: I read with interest the comments of Drs Shapiro and Verma.

They suspect that missing the correct diagnosis of bipolar disorder or unrecognized underling bipolarity in patients could explain the phenomena of resistance to antidepressants (AD), as well as the emergence of dysphoria with chronic AD use. They also hypothesize that AD-induced dysphoria could represent accelerated rapid cycling.

I fully understand their suspicions. Actually, I had the same suspicion when I visited the patients. However, I did not find lifetime hypomania in 6 patients. Two patients presented hypomania in the past, and 1 patient presented hypomania only under AD. I am still treating 7 of these patients, and none of them have presented hypomania, mixed state, or rapid cycling in the last months. Talking with the patients and their relatives, I stressed the importance of getting reliable information on this crucial point. What could be done to recognize underlying bipolarity or rapid cycling?

According to Shapiro and Verma, patients’ response to lithium indicates underlying bipolarity. If we consider the response to lithium highly specific, their comment is right. But, is it so? Does any classification system of mental disorders consider a favorable response to lithium a diagnostic criterion? No, the specificity of response to lithium is not enough. Excellent responses to lithium have been described in patients with severe psychiatric disorders different from bipolar disorder. According to Van Putten and Sanders, a lithium trial is recommended for all the “backward” or intractable psychiatric patients. Furthermore, lithium could have been beneficial to these patients not for a direct therapeutic effect on their illness, but through its neuroprotective properties, reducing the impact of the presumptive alterations induced by AD treatment. Again, the model of tardive dyskinesia (TD) is suggestive because lithium seems to protect against TD. Actually, Drs Shapiro and Verma raise significant questions: Are we able to distinguish unipolar and bipolar depression reliably? Are current diagnostic criteria of mood disorders valid? Is it useful to define “accelerated rapid cycling” cases not fulfilling criteria for mixed episodes or presenting continuous chaotic mood symptoms? I share with them these doubts.

However, the reported cases raise a different question: Does long-term AD treatment induce late-onset neurobiological alterations? Many drugs induce neurobiological adjustments in the long term, as indicated by disparate clinical phenomena such as tolerance and dependence induced by benzodiazepines, barbiturates, opiates, and alcohol; supersensitivity to naltrexone in chronic opioid addicts; increase in the minimal effective antipsychotic dose, supersensitivity psychosis, TD after treatment with antipsychotics; dyskinesia after l-dopa treatment; sensitization to the adverse effects in cocaine abusers; tolerance to drugs and rebound chronic headache in patients with migraine who overuse analgesics; and worsening of epilepsy in patients who discontinue anticonvulsants that do not induce tolerance and dependence.

These phenomena were easily identified because they present with motor symptoms (dyskinesia, TD, epilepsy) or present and disappear in the short term, in almost all patients, with stereotyped features, allowing patients to be controls of themselves (tolerance, sensitization), or never present without a long-term drug exposure (addiction).

Distinguishing treatment complications from the spontaneous course of depression is much more difficult, because mood disorders can present with multiform aspects. However, the sudden, unexpected, and apparently irreversible change in response to AD after years of excellent response, with complete remission of symptoms, raises the doubt of iatrogenic effect.

Hopefully, future research will indicate the frequency of the phenomenon described in this case series and the different clinical features of depression in drug-naïve patients or those with a long history of AD treatment.

**AUTHOR DISCLOSURE INFORMATION**

The author declares no conflicts of interest.

**REFERENCES**