Letters to the Editor

Apologies and Thanks to Reviewers

Regrettably, the names of six reviewers were omitted from our 1997 Reviewer List.1 The prominence the Journal has achieved in the field is a direct outgrowth of the talent and commitment of our reviewers. Their work is selfless except for the one annual occasion when their contributions are recognized in our peer review tribute. To six individuals, I offer both profound apologies and sincerest thanks. Our failure to acknowledge their dedication does not diminish the magnitude of their contribution.

Jonathan O. Cole, M.D.
Mario Cruz, M.D.
Anand P. Popli, M.D.
Sheldon H. Preskorn, M.D.
Duane G. Spiker, M.D
William C. Wirshing, M.D.

REFERENCE


—A.J.G.

Second Thoughts About Clozapine as a Treatment for Neuroleptic-Induced Akathisia

Sir: Recently, Spivak et al.1 published an article in the Journal titled “Clozapine treatment for neuroleptic-induced tardive dyskinesia, parkinsonism, and chronic akathisia in schizophrenic patients.” The issue of finding an effective treatment for chronic treatment-resistant extrapyramidal side effects and akathisia is of considerable clinical importance. Various authors have proposed that clozapine may be useful in treating such patients based on case reports and open studies.2–4 However, before it is concluded that clozapine is effective for such an indication, there is a need for a well-designed controlled study adding clozapine or placebo to ongoing conventional neuroleptic drug treatment.

In 1993, we reviewed 51 hospitalized psychotic patients receiving clozapine in a state hospital, of whom 8 were excluded for either refusal to participate or an inadequate length of clozapine treatment. Our group5 published data on 29 of the remaining 43 subjects (28 had either chronic schizophrenia or schizoaffective disorder, and 1 had atypical psychoses) who received clozapine monotherapy (mean ± SD = 517 ± 136 mg/day) for at least 4 months in stable doses. The remaining 14 patients (who had either chronic schizophrenia or schizoaffective disorder) were treated with a combination of clozapine (mean ± SD = 521 ± 149 mg/day) and conventional neuroleptic drugs (range of chlorpromazine equivalent daily dose between 300 and 500 mg). Seven percent of the clozapine monotherapy group were rated as having akathisia by the Barnes Rating Scale for Drug-Induced Akathisia, whereas 36% of the clozapine and neuroleptic group were rated as having akathisia (Fisher’s exact test, two-tailed, p < .03). The higher rate in the combined treatment group is similar to those reported with neuroleptic drugs by Ayd.5

Even though we do not have baseline scores of the patients’ akathisia ratings, our clinical records show that there was no difference as to the presence or the severity of the baseline akathisia. As a matter of fact, patients with severe akathisia were preferentially receiving clozapine monotherapy, thus we have no reason to believe that the subgroup with the combination therapy had a higher frequency or severity of baseline akathisia. These data do not support a role for clozapine in the treatment of conventional neuroleptic-induced akathisia.

Until definitive studies are done, it may be argued that clozapine seems to show positive results simply because the subjects are no longer receiving conventional neuroleptic drugs, which are associated with much higher rates of extrapyramidal side effects and akathisia than clozapine (see also reference 3).

REFERENCES


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Clozapine-Induced Eosinophilia: Subsequent Neutropenia and Corresponding Allergic Mechanisms

Sir: Galletly et al.1 describe a patient treated with clozapine who had severe eosinophilia (55% of WBCs) followed by neutropenia (neutrophil count of 1840/µL) 7 days later. We report a similar case of a clozapine-treated patient who developed eosinophilia (47% of WBCs) and subsequent neutropenia (neutrophil count of 1800/µL) 6 days later.

REFERENCE


—J.C.L.
Case report. Ms. A, a 30-year-old woman, was given clozapine 200 mg/day for a first episode of paranoid schizophrenia (DSM-III-R) not only because perazine and flupentixol were unable to alleviate her symptoms, but because severe extrapyramidal side effects appeared during treatment with flupentixol. Results of blood studies were within normal limits at the start of treatment, but the eosinophil count was 32% (1000/µL) on day 22, 26% (1010/µL) on day 25, and 47% (1320/µL) on day 26. Neuroleptic medication was stopped to determine whether it was the cause of these changes. On day 28, the eosinophil count decreased to 40% (1300/µL), to 35% (720/µL) on day 30, and to 9% (220/µL) on day 45. During treatment, the total WBC count ranged between 3300 and 8800/µL. The eosinophil peak (day 26) preceded a neutropenic low of 1800/µL (day 32) 6 days later. Clozapine was discontinued on day 26 of treatment.

Ms. A also received iron and biperiden (the latter during only the first days of clozapine treatment) as concomitant medication. Between days 23 and 25, acetaminophen was administered because of toothache. Her body temperature was below 37°C, and Ms. A remained free of symptoms. No allergies or other eosinophilia-associated disorders were found on examination or were present in the medical history. We studied some immunologic parameters (immune globulins, collagen antibodies, and other autoantibodies) and found that only IgE had increased (254.0 IU/dL, reference value < 120.0 IU/dL). No ova or parasites were detected in two stool specimens.

Eosinophilia is one of the possible white blood cell abnormalities (e.g., leukopenia, agranulocytosis, leukocytosis) associated with clozapine use. Hummer et al. reported a transient eosinophilia in 62% of 68 patients treated with clozapine. Banov et al. found a higher risk of eosinophilia for women than for men in a review of 118 case histories (23% vs. 7%). Krupp and Barnes also reported a higher female risk for clozapine-induced agranulocytosis. Eosinophilia usually occurs between weeks 3 and 5 of clozapine administration and disappears after another 4 weeks. The highest eosinophil count reported thus far was 55% of the WBCs.

Eosinophilia during treatment with clozapine has sometimes been accompanied by several other clinical abnormalities: diarrhea and fever; diarrhea, fever, and a left shift of the WBCs; pancreatitis; and eosinophilic colitis. Whether a high eosinophil count indicates that clozapine treatment should be discontinued is unclear. Banov et al. recommended close monitoring, provided no other abnormalities occurred. Tiihonen and Paanila proposed stopping clozapine when eosinophil counts were greater than 1400/µL. In the latest Novartis guidelines (Wander, communication, May 1996), discontinuation of clozapine when the patient’s eosinophil counts are above 3000/µL is recommended. Recently, in a prospective study of 107 patients, Hummer et al. investigated whether eosinophilia during clozapine treatment has predictive value for subsequent neutropenia/ agranulocytosis. Patients with eosinophilia showed a decrease in neutrophil count (< 2000/µL neutrophil granulocytes) significantly more often than patients without eosinophilia. Eosinophilia predicted neutropenia with a sensitivity of 83.3% (95% confidence interval [CI] = 51.6% to 97.0%) and a specificity of 46.3% (95% CI = 36.0% to 56.8%). They, therefore, suggested that eosinophilic patients should be given more attention than patients without eosinophilia. Eosinophilia caused neutropenia by means of a mechanism involving prostaglandin E.

Druss and Mazer stated that eosinophilia during clozapine treatment might represent a benign allergic reaction to the drug. Our finding of an elevated IgE level seems to support this. Furthermore, eosinophils can possibly cause neutropenia by means of a distinct disadvantage for a patient with an increasing eosinophil count. An uncontrolled withdrawal of the drug could deprive a patient of the benefits of clozapine. Therefore, the decision to discontinue treatment should be made for each patient individually.

On the basis of the literature and our own case, we reached the following conclusions: (1) Eosinophilia arising during treatment with clozapine is common, and eosinophil counts can reach more than 50% of the WBC count. (2) Clozapine-induced eosinophilia can occur solely or in association with other clinical abnormalities like colitis or pancreatitis. (3) Recently, Tiihonen and Paanila suggested that clozapine should be discontinued when eosinophil counts are above 1400/µL: the guidelines of Novartis propose the same when the count reaches 3000/µL. However, since there is no clear evidence for a distinct disadvantage for a patient with an increasing eosinophil count, an uncontrolled withdrawal of the drug could deprive a patient of the benefits of clozapine. Therefore, the decision to discontinue treatment should be made for each patient individually. (4) An allergic cause has also been proposed. Our finding of a high IgE seems to be in concert with this. A thorough investigation of allergy-related parameters is needed. (5) Since neutropenia/ agranulocytosis is the main disadvantage with clozapine treatment, reliable predictors would be of great value to enhance its safety margin. However, Hummer et al. reported that eosinophilia is a moderate predictor of impending neutropenia. Other variables seem to be involved since eosinophilia in many instances causes no changes. A gender-related factor might be worth investigating since both eosinophilia and agranulocytosis are more prevalent in females.

REFERENCES

Sir: For patients admitted to a psychiatric hospital, disturbances in thinking, mood, and perception have strong diagnostic relevance. However, especially in schizophrenia, the physical appearance of patients might be of clinical importance. This is illustrated by a number of case reports and small series of studies in which schizophrenic patients were found to have shaved their heads or cut their hair just before or during admission. Apart from this hair-cutting phenomenon, redundant clothing (wearing multiples of the same item) is mentioned in connection with psychosis. One study found that “wearing redundant clothes appears to be a readily observable behavior associated with schizophrenia in the emergency room.”

Perhaps, then, drastic changes in physical appearance are early signs of decompensation. To explore this issue in more detail, we interviewed members of the self-help group “Anoiksis” at one of its monthly meetings. Anoiksis is the Dutch patient association for chronic psychotic or schizophrenic people. We expected that members of this organization would have more insight into their disorder than would hospitalized patients. Eleven members were present at the meeting, and they were asked whether they recalled making significant changes in their appearance (e.g., hair, clothing) and, if so, what the meaning of these changes could be. All of them, at the time of the interview, fulfilled the DSM-IV criteria for schizophrenia. More importantly, they warrant systematic study. Also, it would be relevant to examine the connection between schizotypy and drastic changes in physical appearance in a community sample.

REFERENCES

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Family History and Early Psychotogenic Response to Marijuana

Sir: Marijuana use has been associated with mental illness for more than a century and a half. This relationship was first noted by J. J. Moreau de Tours in his 1845 classic work, Hashish and Mental Illness. Observations by Indian psychiatrists kept the topic alive during the first half of this century. With the increased availability of “street drugs” in the 1960s, marijuana became the most frequently abused drug with the exception of ethyl alcohol. Only a small proportion of those who use marijuana or other psychotogenic drugs develop an episode of severe mental illness (e.g., psychosis, mania). We have been interested in the risk factors for such a response, for these individuals do not usually have poor premorbid histories indicating classical schizophrenia or related disorders. We have previously reported some observations which suggest that family history and amount of drug use may be reciprocally related in the production of psychosis. That is, when family history is strongly positive for major mental illness, only minimal drug use may be required to produce psychosis or mania. We have recently observed 4 cases of early psychotogenic response to marijuana, and we were able to obtain family history data using the family history method in each instance. Diagnoses were made according to DSM-IV criteria using all available clinical data.

Case 1. Mr. A, a 20-year-old single man, was admitted to the hospital because of a recent (1 week before) onset of delusional ideas and auditory hallucinations of a grandiose and religious nature after his first use of marijuana (he reported smoking approximately 6 cigarettes over a 2-day period), in the context of a breakup with his girlfriend. There was no other drug use by report, and urine was positive for cannabinoids. There was no prior psychiatric history, and his developmental milestones had been normal to that point. His mother had been diagnosed as having bipolar disorder and was being treated with lithium. The working diagnosis of Mr. A was mania with psychotic features. Remission of symptoms required the administration of perphenazine 42 mg/day and lithium carbonate 1200 mg/day for 2 weeks.

Case 2. Mr. B, an 18-year-old single man, was transferred from another hospital following 2 weeks of grandiose delusions after a 1-week period of heavy marijuana use during a European trip. He had for the first time smoked several hashish “pipes” each day for several days before the onset of his symptoms. He denied use of other drugs. There was no prior psychiatric history, and his developmental milestones had been normal to that point. His mother was known to have bipolar disorder and had been treated with lithium for 10 years. Mr. B’s clinical diagnosis was mania with psychotic features. Urine was positive for cannabinoids. Haloperidol 8 mg/day and lithium carbonate 1500 mg/day controlled his symptoms after approximately 10 days of treatment.

Case 3. John, a 15-year-old adolescent, was admitted to the hospital after experiencing delusions and auditory hallucinations for 2 days in the context of his first marijuana use. He reportedly had smoked 3 to 5 marijuana-containing cigarettes per day for 3 days before the onset of symptoms. He denied using other drugs. There was no prior formal psychiatric history, although there was a record of poor school performance. Urine toxicology screen was positive for cannabinoids. Otherwise, social development appeared normal for his age. His mother had been diagnosed as schizoaffective, manic type and was being treated with fluphenazine and lithium. John’s clinical diagnosis was psychosis, not otherwise specified. Haloperidol 8 mg/day led to satisfactory symptom control after 1 week of treatment.

Case 4. Ms. C, an 18-year-old woman, was admitted to the hospital with a 1-week history of delusions and auditory hallucinations after smoking 2 marijuana-containing cigarettes in the context of a second-trimester abortion 1 month before the onset of her symptoms. She reported apparently normal social development and no prior psychiatric history. There was no history of use of other illicit drugs. Urine was positive for cannabinoids. Her mother had had a postpartum manic illness that required treatment with a neuroleptic and lithium. Ms. C’s working diagnosis was psychosis, not otherwise specified. She was treated successfully with haloperidol 15 mg/day.

These 4 patients developed a psychotic disorder requiring hospitalization and neuroleptic treatment after smoking relatively small amounts of marijuana for the first time. Similar observations have been made previously by a number of observers. For example, Talbott and Teague reported 32 cases of acute psychosis after alleged first marijuana use; however, family history data were not obtained. Kaplan reported 5 cases of acute and persistent psychosis after first marijuana use. Two of these subjects had a parent diagnosed as having “borderline schizophrenia.” Pålsson and coworkers described 11 cases of cannabis psychosis in association with longer periods of prepyschotic cannabis use, but emphasized the low incidence of a positive family history of mania or psychosis. McGuire et al. studied 23 patients with acute psychosis who were cannabino-positives on urinary screening. They found a significantly greater familial morbid risk of schizophrenia in these subjects’ first-degree relatives compared with the relatives of cannabis-negative psychotic subjects.

Our subjects were apparently uniquely susceptible to the psychotogenic effects of cannabis, since they developed persistent psychoses after the first use of relatively small amounts of the drug. Each subject’s mother had been diagnosed with manic disorder. 2 with psychotic features. Mania may be associated with excessive dopaminergic neurotransmission. Cerebrospinal fluid homovanillic acid (HVA) has been reported to be increased in patients with mania. Elevated pretreatment plasma HVA predicts a favorable neuroleptic response in mania with psychotic features. Recently, the dopamine transporter has been considered as a possible susceptibility locus for bipolar disorder. Marijuana is a dopamine agonist, and its use may precipitate illness in subjects genetically vulnerable to psychotic affective disorder or schizophrenia. A positive family history for mania or psychosis in first-degree relatives may indicate that experimentation with marijuana should be avoided.

REFERENCES

Serotonin reuptake inhibitors (SRIs) commonly impair aspects of sexual function. Although many neurotransmitters may play roles in the pathophysiology of sexual dysfunctions, the most successful antideses to these dysfunctions are believed to exert their effects through central nervous system enhancement of dopamine neurotransmission or reduction of serotonin neurotransmission. Mediations such as amantadine, bupropion, stimulants, yohimbine, cyproheptadine, and buspirone have alleviated various types of antidepressant-induced sexual dysfunctions, but we believe this report is the first to describe an effective remedy for antidepressant-induced genital anesthesia.

EGB, produced from green-picked leaves of the Ginkgo biloba tree, has been valued for medicinal properties in China for over 2 millennia. It has been used as an herbal remedy for short-term memory loss, headache, tinnitus, and depression. More recently, EGB has been reported to improve sexual desire, arousal, and orgasmic function in patients who experienced impairment associated with the use of SRIs. The mechanism for these beneficial effects on sexual function is not yet clear but may include vasodilatory or antioxidant effects, actions upon platelet activating factor (PAF), prostaglandins, norepinephrine, serotonin, monoamine oxidase, acetylcholine, or nitric oxide. At standard dosages of 60 to 360 mg/day, the side effects have usually been limited to gastrointestinal disturbances, headache, and “general CNS activation.” EGB’s effects on PAF and the suspected association of spontaneous bilateral subdural hematomas with chronic EGB use in one patient suggest caution in its use, despite subsequent questioning of the strength of this association. Concern regarding anesthetic effects would be amplified when EGB is coprescribed with enhancers of serotonergic neurotransmission such as SRIs, because SRIs themselves have been associated with increased risk for bleeding in some patients, although the precise mechanism for such an effect has so far eluded explanation.

The improvement in this patient’s genital anesthesia appears temporally associated with use of EGB, but this uncontrolled case report cannot refute with certainty the possibility that she improved spontaneously. Because antidepressant-induced sexual dysfunctions impair patients’ quality of life and reduce compliance with treatment, more rigorously controlled double-blind investigation of EGB and other potential remedies for antidepressant-induced sexual dysfunctions is desired.

REFERENCES

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8. White HL, Scates PW, Cooper BR. Extracts of Ginkgo biloba leaves inhibit monoamine oxidase. Life Sci 1996;58:1315–1321

Fluoxetine-Induced Genital Anesthesia Relieved by Ginkgo biloba Extract

Sir: Among the many published cases of antidepressant-induced sexual dysfunction, a relatively infrequently reported phenomenon is genital anesthesia, the diminution or loss of pain, pressure, and touch sensations in the vulvovaginal area or penis. Genital anesthesia has been associated with fluoxetine treatment in one woman, whose vulvovaginal anesthesia was confirmed by “needle prick” testing. A man receiving fluoxetine 20–60 mg/day developed numbness of the glans penis. Each of these reports notes the successful treatment of depression by fluoxetine and the gradual resolution of genital anesthesia after fluoxetine discontinuation. In neither case was an apparent alleviation of fluoxetine-induced female genital anesthesia in one patient by administration of Ginkgo biloba extract (EGB 761).

Case report. Ms. A, a 37-year-old woman, received fluoxetine treatment for an episode of major depressive disorder. Her sexual functioning, which had previously been normal, was not impaired by her depression. Once fluoxetine was begun, initially at 10 mg/day and gradually increased to 60 mg/day, she quickly noted diminished desire, reduced arousal (with decreased lubrication), and delayed orgasm. Furthermore, she noted altered sensation in her vagina, vulva, and clitoris such that touch was perceptible but reduced in intensity and “not stimulating.” Repeated trials of yohimbine 5.4 mg or cyproheptadine 4 mg taken 1 hour before sexual activity failed to affect her symptoms.

After 2 weeks of daily use, EGB (180 to 240 mg/day) taken with fluoxetine (60 mg/day) improved her level of desire, reestablished arousal with lubrication, and reversed the delay of her orgasms while restoring her previous level of vaginal, vulvar, and clitoral sensation. She has continued to take EGB and has noted no bruising, bleeding, or other adverse effects. Before her depression and sexual dysfunction, she had been taking a birth control pill (Tri-Levlen 28, a phasic combination regimen consisting of 6 days of levonorgestrel 0.050 mg and ethinyl estradiol 0.030 mg, 5 days of levonorgestrel 0.075 mg and ethinyl estradiol 0.040 mg, 10 days of levonorgestrel 0.125 mg and ethinyl estradiol 0.030 mg, and 7 days of inert pills) and an antiestrogen, cetirizine 10 mg/day. She took these medications consistently throughout her depressive episode, sexual dysfunction, and improvement with EGB. She remains on treatment with EGB at this time.

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Corrections

In the article “The Effects of Risperidone on the Five Dimensions of Schizophrenia Derived by Factor Analysis: Combined Results of the North American Trials” by Stephen R. Marder, M.D., et al. (1997;58:538–546), the column of F values in Table 1 (page 540) should be placed to the right of the column for Adjusted Mean Changes in Scores. Also in Table 1, the total PANSS adjusted mean change in scores for placebo should be 3.8. In Figure 3 (page 544), the change score for the risperidone 6–16 mg/day group for Factor 4 should be labeled as significant at p < .01. The corrected Table 1 and Figure 3 are reproduced here.

The staff regrets these errors.