Letters to the Editor

Mannitol-Induced Acute Manic State

Sir: We present an interesting case of possible mannitol-induced manic state in a depressed elderly woman.

Case report. Ms. A, a previously well-adapted 75-year-old woman without personal or family history of mental disorders, presented with a first episode of severe major depression (DSM-IV criteria). On the 10th day of antidepressant treatment with nortriptyline, 50 mg/day, a diagnosis of bilateral acute angle closure glaucoma was made. Continuous intravenous infusion of mannitol 20% (500 cm^3 in 1 hour), oral acetazolamide (500 mg), and topical treatment with pilocarpine 2% (1 drop/15 min), timolol 0.50% (1 drop/15 min), and dexamethasone 0.1% (1 drop/15 min) were prescribed simultaneously. Thirty minutes later, when her pain had diminished, Ms. A became euphoric, and she remained overactive, overly affectionate, and talkative, showing pressured speech and flight of ideas and telling jokes. Her manic state remitted in 1 hour after cessation of mannitol infusion, and her severe depression came back dramatically.

In a search for potential causes of secondary manic states, an exhaustive laboratory evaluation (with toxicologic screening included) and a careful medical examination were carried out. At no time was Ms. A febrile, and no evidence of cognitive impairment, hallucinations, or fluctuation in her level of consciousness was observed. No neurologic deficits were present. No metabolic dysfunction seemed to be related to these symptoms, and electroencephalogram showed no disturbance. Cranial magnetic resonance imaging revealed unspecific mild subcortical and cortical atrophy. Her plasma nortriptyline level was 65 ng/mL.

Ms. A's major depression was treated with electroconvulsive therapy, and 1 year later, no further mania or depression had appeared. She is currently taking venlafaxine, 150 mg/day.

On the basis of the lack of abnormal findings in medical examination and complementary diagnostic proofs, we considered that Ms. A's manic state might be associated with her medications.[1,2] Assuming that there are 15 drops/mL and that 100% systemic absorption is improbable, we believe that the total dose of drugs administered by topical application was very low and not enough to cause mania. Manic features induced by pilocarpine or corticosteroids have been described,[3,4] but daily and higher doses were used. With regard to acetazolamide, pharmacokinetic data show that plasma drug levels after oral treatment peak at 2 hours,[5] after manic state has already abated. Euphoria following daily nortriptyline treatment has been described as well,[6] but the rapid and spontaneous regression of manic symptoms in the present case makes this option unlikely. For all of these reasons, it appears that intravenous mannitol may have provoked the episode of mania, particularly if we consider that progressive remission of manic symptoms was observed after discontinuation of intravenous infusion of mannitol and that the intensity of manic symptoms correlated with expected plasma mannitol levels. Mannitol levels were indirectly measured in osmolality: 325 mmol/kg H$_2$O (normal range, 275–295 mmol/kg

H$_2$O) when she started showing manic symptoms, and 302 mmol/kg H$_2$O 1 hour later, when mania progressively regressed.

Mannitol infusion can lead to both an acute expansion of extracellular fluid volume and a rapid reduction of intracellular fluid volume with retention of brain electrolytes.[7] Although mechanisms implicated in the pathogenesis of secondary mania have not been established in the present case, the sudden appearance of central nervous system hypernatremia and hyperosmolality may best explain the clinical presentation and course of this patient. For this reason, mannitol should be considered a potentially mania-inducing drug.

REFERENCES

1. Evans DL, Byerly MJ, Greer RA. Secondary mania: diagnosis and treatment. J Clin Psychiatry 1995;56(suppl 3):31–37
2. Peet M, Peters S. Drug-induced mania. Drug Saf 1995;12:146–153
3. Waters BGH, Lapierre YD. Secondary mania associated with sympathomimetic drug use. Am J Psychiatry 1981;138:837–838
4. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes: a report of 14 cases and a review of the literature. J Affect Disord 1983;5:319–322
5. Preisig PA, Toto RD, Alpern RJ. Carbonic anhydrase inhibitors. Renal Physiol 1987;10:136–159
6. Peet M. Induction of mania with selective serotonin reuptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994;164:549–550
7. McManus ML, Strange K. Acute volume regulation of brain cells in response to hypertonic challenge. Anesthesiology 1993;78:1132–1137

Víctor Navarro, M.D.
Eduard Vieta, M.D.
Cristóbal Gastó, M.D.
Hospital Clínic de Barcelona
Barcelona, Spain

Sexual Dysfunction and Fluvoxamine Therapy

Sir: With interest we read the study by Nafziger et al.[1] (March 1999 issue) and their replies to the letters of Banov[2] (December 1999 issue) and Laird[3] (January 2000 issue) regarding the incidence of sexual side effects of fluvoxamine. Nafziger et al.[1] claim that the incidence of fluvoxamine-induced sexual side effects is comparable with the rates of the other selective serotonin reuptake inhibitors (SSRIs). However, the open-label design and lack of a placebo-control group in the study of Nafziger et al.[1] make generalization of their conclusion inappropriate and may mislead readers. In their study, sexual dysfunction was assessed by a questionnaire.

We are of the opinion that for comparative sexual pharmacologic studies, accurate instruments and objective methods need to be used. For measurement of erectile function, lubrication, and ejaculation, these instruments are available. However, because of a lack of an empirical, operationalized definition, the very subjective feelings of libido still remain to be measured by a questionnaire, which makes investigation of the intensity of

medication-induced libido changes in particular less accurate. Unfortunately, accurate instruments are hardly used in psychiatric sexual pharmacologic studies. As a consequence, there is a paucity of hard evidence for differences among psychoactive drugs in their effects on erection and lubrication. However, this is not the case for the ejaculation process. Using a stopwatch as an accurate instrument, we have conducted human[4] and animal[5] studies demonstrating that fluvoxamine indeed differs from other SSRIs, particularly from paroxetine, in the extent that it delays ejaculation.

It is not the frequency of sexual side effects but rather their intensity that disturbs a patient's sexual life.

In a double-blind placebo-controlled study[4] in mentally, physically, and sexually healthy men with lifelong rapid ejaculation we investigated the ejaculation delay induced by paroxetine, 20 mg/day; fluoxetine, 20 mg/day; sertraline, 50 mg/day; and fluvoxamine, 100 mg/day. For that purpose, the female partners measured the Intravaginal Ejaculation Latency Time (IELT), defined as the time between the start of vaginal intromission and the start of intravaginal ejaculation, of their male partners using a stopwatch during various occasions of intercourse at home for a 4-week baseline period. A key point in our methodology is that we wanted to have equal baseline values of the ejaculation time of the participating men. Therefore, only men with an IELT of less than 1 minute were included after baseline measurement. After randomization, these men continued to measure their IELT at home for a period of 6 weeks. This study demonstrated that fluvoxamine and placebo had a mild delaying effect on ejaculation (1.9-fold and 1.5-fold increase, respectively) compared with the other SSRIs (4.4- to 7.8-fold increase). In a similar double-blind placebo controlled study[4] in men with rapid and less rapid ejaculation, paroxetine showed an identical percentage increase in ejaculation delay in both groups (approximately 400%), indicating that data derived from studies in men with rapid ejaculation can be extrapolated to those with less rapid ejaculation.

We replicated these human findings in male rats. In a vehicle-controlled study,[5] we compared the effects of fluvoxamine (30 mg/kg) and paroxetine (10 mg/kg) on male rats' sexual behavior. After daily oral administration, paroxetine but not fluvoxamine inhibited sexual behavior, including ejaculation latency, significantly on day 7; this effect was even further statistically significantly enhanced at day 14 (p < .001).

No adequate explanation can be offered yet for the differential effects of SSRIs on ejaculation. It can be speculated that, although SSRIs have the same mechanism of action, i.e., blockade of serotonin (5-HT) reuptake, different SSRIs enhance 5-HT release differentially at different places in the central nervous system, thereby stimulating certain postsynaptic 5-HT receptors to a different extent.[6] Animal studies have clearly demonstrated that activation of 5-HT_{1A} receptors shortens ejaculation time, whereas activation of 5-HT_{2C} receptors delays ejaculation.[6] Indeed, a conditioned taste aversion procedure in mice demonstrated that 5-HT_{1A} receptors are primarily involved in the stimulus effects of fluvoxamine and that 5-HT_{2C} receptors are primarily involved in the stimulus effects of fluoxetine.[7] However, apart from the involvement of central 5-HT metabolism in ejaculation, other unknown mechanisms may play a role in the differential effects of SSRIs on ejaculation.

With the same stopwatch approach, we conducted another human study[8] which demonstrated that citalopram, 20 mg/day, also had significantly less delaying effect on ejaculation than did paroxetine, 20 mg/day (1.8- and 9.1-fold increase, respectively).

Both the clinical observations of Banov[2] in psychiatric patients treated with fluvoxamine and, interestingly, the study of Nafziger et al.[1] in healthy volunteers showed few male subjects

who experienced delayed ejaculation, except one man who had concomitant erectile difficulties. So, in spite of their conclusion, the study of Nafziger et al.[1] is indirectly in correspondence with our findings that fluvoxamine has less effect on ejaculation than other SSRIs. The clinical relevance of our studies is that patients who suffer from unwanted SSRI-induced ejaculation delay may be switched to fluvoxamine or citalopram. This will probably result in an improved ease in ejaculation.

REFERENCES

1. Nafziger AN, Bertino JS Jr, Goss-Bley AI, et al. Incidence of sexual dysfunction in healthy volunteers on fluvoxamine therapy. J Clin Psychiatry 1999;60:187–190. Correction 1999;60:341
2. Banov MD. Improved outcome in fluvoxamine-treated patients with SSRI-induced sexual dysfunction [letter with reply]. J Clin Psychiatry 1999;60:866–868
3. Laird LK. Sexual dysfunction on fluvoxamine therapy [letter with reply]. J Clin Psychiatry 2000;61:62–63
4. Waldinger MD, Hengeveld MW, Zwinderman AH, et al. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine and sertraline. J Clin Psychopharmacol 1998;18:274–281
5. Waldinger MD, van Oorschmot R, Veening J, et al. SSRIs and sexual behavior in male rats: differential effects of paroxetine and fluvoxamine. In: New Research Program and Abstracts of the 152nd Annual Meeting of the American Psychiatric Association; May 20, 1999; Washington, DC. Abstract NR713:270
6. Waldinger MD, Olivier B. Selective serotonin reuptake inhibitors (SSRIs) and sexual side effects: differences in delaying ejaculation. In: Sacchetti E, Spano P, eds. Advances in Preclinical and Clinical Psychiatry, vol 1. Milano, Italy: Excerpta Medica; 2000:117–130
7. Gommans J, Bouwknecht JA, Hijzen TH, et al. Stimulus properties of fluvoxamine in a conditioned taste aversion procedure. Psychopharmacology (Berl) 1998;156:1310–1315
8. Waldinger MD, Zwinderman A, Olivier B. SSRIs and ejaculation: a double-blind, randomized, comparative fixed-dose study with paroxetine and citalopram. In: New Research Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 18, 2000; Chicago, Ill. Abstract NR685:242–243

Marcel D. Waldinger, M.D., Ph.D.
Leyenburg Hospital
The Hague, the Netherlands
Berend Olivier, Ph.D.
Yale University School of Medicine
New Haven, Connecticut

Dr. Nafziger and Colleagues Reply

Sir: We appreciate the insightful comments of Drs. Waldinger and Olivier. While we agree that objective measurements of sexual function are potentially more accurate and useful than self-report questionnaires, it is difficult (and for most clinicians, impossible) to implement objective measurements in clinical practice.

We agree that it is unfortunate that accurate instrumental tools (including standardized questionnaires) are seldom used in psychiatric sexual pharmacologic studies. In fact, they are seldom used in any pharmacologic studies.

Drs. Waldinger and Olivier cite interesting animal data in support of their hypothesis. These data suggest a differential effect of citalopram, fluoxetine, fluvoxamine, and paroxetine on sexual functioning in healthy male humans and male rats. These data add to our understanding of the influence of selective serotonin reuptake inhibitors (SSRIs) on male sexual functioning and, in particular, ejaculation.

Our study did not attempt to compare SSRIs with respect to their effect of delayed ejaculation. In fact, the small number of

male subjects (N = 10) in our study makes it unlikely that we could demonstrate such an effect even if it were present. We must therefore disagree with the conclusion that our data support the finding that fluvoxamine has less effect on ejaculation than other SSRIs.

Anne N. Nafziger, M.D., M.H.S.
Joseph S. Bertino, Jr., Pharm.D.
Angelica I. Goss-Bley
Bassett Healthcare
Cooperstown, New York
Angela D. M. Kashuba, B.Sc.Phm., Pharm.D.
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Priapism Associated With Polypharmacy

Sir: Priapism is sustained and painful erection that may be seen as an adverse effect of atypical antipsychotics, including risperidone[1–4] and olanzapine.[2,5–7] Although it is relatively rare, its incidence may be increased through polypharmacy. We report the case of a 37-year-old man who developed priapism during concomitant administration of risperidone, olanzapine, and fluvoxamine.

Case report. Mr. A, a 37-year-old biracial man, had a 19-year history of schizophrenia and obsessive-compulsive disorder (OCD) (DSM-IV). He had extensive exposure to antipsychotics including trifluoperazine, molindone, haloperidol, risperidone up to 6 mg/day, olanzapine up to 15 mg/day, clozapine up to 300 mg/day, and quetiapine up to 500 mg/day, with only partial responses. His history also included treatment with clomipramine, fluvoxamine, and benzodiazepines for OCD symptoms, which responded only partially to combined pharmacologic and behavioral therapies. Because of the severity of his psychiatric symptoms, Mr. A had been hospitalized continuously for 1 year. His medical history was positive for headaches and daltonism (color blindness). Medical workup, including a recent magnetic resonance imaging of the head, was unremarkable. He had never experienced priapism previously.

Mr. A was eventually treated with gabapentin, 900 mg/day; oxazepam, 25 mg/day; fluvoxamine, 300 mg/day; olanzapine, 7.5 mg/day; and risperidone, 6 mg/day, with noticeable improvement in both his psychotic and obsessive-compulsive symptoms. However, he developed his first episode of priapism after 3 months on treatment with this combination. The priapism was characterized by a painful erection lasting 4 hours that resolved after emergency treatment by intercavernous injections of phenylephrine. No medication changes were made following this initial episode because of the overall clinical improvement. Olanzapine was discontinued 3 days later after a second episode of priapism occurred. The patient had 3 more episodes of priapism over the following 2 weeks, requiring the same emergency department treatment. Because of increased psychotic symptoms, olanzapine was restarted after this 2-week period. Terbutaline was initiated after consultation with a urology physician, and no further episodes of priapism occurred.

The most likely etiology for Mr. A's priapism is pharmacologic, given the absence of medical findings or trauma. Risperidone is thought to cause priapism because of its high affinity for α_1-adrenergic receptors, producing a relative decrease in local sympathetic tone compared with local parasympathetic tone.[1,5] Olanzapine's α_1-adrenergic antagonism has also been linked to

priapism.[3,4] In addition, risperidone and olanzapine exert α_2 antagonism that stimulates production of nitric oxide, a potent smooth muscle relaxant affecting afferent arterioles and the corpora cavernosa.[4] The fact that Mr. A had been previously treated with each of these medications without developing priapism suggests that an additive effect probably occurred. This effect may have been exacerbated through fluvoxamine-induced inhibition of cytochrome P450 1A2, which has been shown to result in olanzapine levels 3 to 4 times higher than expected.[8,9]

Despite a lack of controlled trials, drug-refractory patients are sometimes treated with 2 antipsychotic drugs. Fluvoxamine is often added to antipsychotic drugs for treatment of patients with psychosis and OCD. Although combined treatment may be effective for some patients, it can increase the risk of potentially serious side effects. Since several antipsychotics have been associated with priapism, clinicians should exercise caution when prescribing drugs with synergistic effects or mechanisms of action. We are calling attention to priapism as an adverse effect that can result from combined regimens.

REFERENCES

1. Maizel S, Umansky L, Knobler HY. Risperidone-induced priapism. Harefuah 1996;130:744–745, 799
2. Weiner DM, Lowe FC. Psychotropic drug-induced priapism: incidence, mechanism and management. CNS Drugs 1998;9:371–379
3. Tekell JL, Smith EA, Silva JA. Prolonged erection associated with risperidone treatment. Am J Psychiatry 1995;51:430–433
4. Emes CE, Millson RC. Risperidone-induced priapism. Can J Psychiatry 1994;39:315–316
5. Gordon M, deGroot CM. Olanzapine-associated priapism [letter]. J Clin Psychopharmacol 1999;19:192
6. Deirmenjian JM, Erhart SM, Wirshing DA, et al. Olanzapine-induced reversible priapism: a case report. J Clin Psychopharmacol 1998;18:351–353
7. Heckers S, Anick D, Boverman JF, et al. Priapism following olanzapine administration in a patient with multiple sclerosis. Psychosomatics 1998;39:288–290
8. Armstrong SC, Gabriel GM, Cozza KL. The cytochrome P450 system: a complete guide to the general and consultation-liaison psychiatrist. Presented at the 44th annual meeting of the Academy of Psychosomatic Medicine; Nov 20–23, 1997; San Diego, Calif
9. Pies R. The cytochromes made simple? (Not.) Psychiatr Times Sept 1997;XIV:14–18

Anca Seger, M.D.
Hepburn Medical Center
Ogdensburg, New York
J. Steven Lamberti, M.D.
University of Rochester
Rochester, New York

Treatment of Tardive Dyskinesia With Donepezil

Sir: Tardive dyskinesia (TD) remains a significant clinical problem for which there is no uniformly effective therapy.[1] The rationale for its treatment with cholinomimetic drugs derives from the conceptualization of TD as the result of an imbalance between cholinergic and dopaminergic systems in the basal ganglia. Unfortunately, the response of TD to treatment with acetylcholine precursors has been inconsistent.[1,2] However, precursors may not increase acetylcholine activity if neurotransmitter synthesis is impaired in presynaptic neurons. In fact, Miller and Chouinard[3] reviewed data which suggest that striatal cholinergic neurons are damaged in patients with TD.

For similar reasons, acetylcholine precursors have been ineffective in treating Alzheimer's disease. In contrast, cholinesterase inhibitors have improved cognition in patients with dementia because these agents increase cholinergic transmission by inhibiting acetylcholinesterase in the synaptic cleft, thereby decreasing hydrolysis of acetylcholine released from surviving presynaptic neurons.[4]

By analogy, cholinesterase inhibitors may also be effective in TD. Although the response of TD to intravenous challenge with the short-acting agent physostigmine has been variable,[1,2,5] Ingram and Newgreen[6] reported a 43% decrease in TD ratings in patients treated with tacrine. Hence, we examined the response to treatment with donepezil, 5 mg/day, for 4 weeks, followed by an additional 2 weeks on donepezil, 10 mg/day, in 3 patients meeting DSM-IV criteria for TD. Baseline total Abnormal Involuntary Movement (AIMS)[7] scores were averaged for 2 rating sessions 2 weeks apart. The TD response using the AIMS was measured at 2-week intervals after donepezil was initiated.

Case 1. Mr. A, a 66-year-old man, had received antipsychotics intermittently over a 10-year period for schizoaffective disorder. He developed involuntary movements affecting his face, tongue, trunk, and extremities 8 years prior to examination. He currently had been receiving stable daily doses of quetiapine, 75 mg; divalproex sodium, 500 mg; and nefazodone, 300 mg, for at least 1 month. His mean baseline AIMS score of 23 decreased to 20, 15, and 18, obtained every 2 weeks during 6 weeks on treatment with donepezil.

Case 2. Mr. B, a 45-year-old man, was diagnosed with schizophrenia and diabetes mellitus. Treated with antipsychotics for more than 10 years, he developed involuntary movements of his face, tongue, and extremities 5 years prior to examination. At the time of study, he had been receiving stable daily doses of olanzapine, 40 mg; trazodone, 200 mg; hydroxyzine, 125 mg; and glipizide, 40 mg, for at least 1 month. His mean baseline AIMS score of 19 decreased to 10, 6, and 5 during 6 weeks on treatment with donepezil.

Case 3. Mr. C, a 39-year-old man, was diagnosed with schizophrenia and had received haloperidol for more than 10 years. Three years prior to examination, he developed involuntary movements of his face and upper extremities. At the time of study, he had been receiving stable daily doses of haloperidol, 15 mg, and temazepam, 30 mg, for at least 1 month, but was also using cocaine. His mean baseline AIMS score of 9 decreased to 4, 2, and 2 during 6 weeks on treatment with donepezil.

We found that treatment for 6 weeks with donepezil, 5 to 10 mg/day, appeared to diminish TD by 22%, 74%, and 78% in 3 patients taking stable doses of antipsychotic medications. No changes were noted in cognition, psychiatric symptoms, or other extrapyramidal signs, and no side effects were reported.

The specificity of the effect of donepezil may be questioned in these cases. One patient had only mild improvement (case 1), which could have reflected random fluctuations of symptoms or variability in ratings. Erratic use of cocaine could have accounted for changes in TD in another patient (case 3).

However, against a random, nonspecific effect was the progressive decline in TD during the first 4 weeks of treatment in each case. Furthermore, the mean ± SE difference between the 2 baseline AIMS scores (2.3 ± 0.9) was exceeded by the decrease in TD ratings of 5, 14, and 7 after initiation of donepezil in cases 1, 2, and 3, respectively. The consistency of ratings is supported by our previous achievement of satisfactory interrater reliability for the AIMS using the intraclass correlation coefficient (0.75).[8] Although a dose-response effect was not observed with 10 mg/day of donepezil, 5 mg/day may have provided

maximum benefit. Alternatively, if 10 mg/day had also been given for 4 weeks or longer, a greater response may have been observed. Although changes in the first patient were modest compared with the others, this patient also had a mood disorder, was older, and had more severe TD for a longer period of time. With donepezil, response may depend on the degree of cholinergic cell loss or damage, which may correlate with age or duration of symptoms.[3] Consistent with previous pharmacotherapy of TD,[5] the response to donepezil may ultimately prove to be heterogeneous between individuals.

Nevertheless, although donepezil appeared to be effective in suppressing TD in these patients, placebo-controlled double-blind trials are required to confirm these findings before donepezil and other recently developed anticholinesterases can be recommended as a promising new strategy in the treatment of this disorder.

REFERENCES

1. Egan MF, Apud J, Wyatt RJ. Treatment of tardive dyskinesia. Schizophr Bull 1997;23:583–609
2. American Psychiatric Association Task Force on Tardive Dyskinesia. Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association. Washington, DC: American Psychiatric Press; 1992
3. Miller R, Chouinard G. Loss of striatal cholinergic neurons as a basis for tardive and L-dopa–induced dyskinesias, neuroleptic-induced supersensitivity psychosis and refractory schizophrenia. Biol Psychiatry 1993;34:713–738
4. Mayeux R, Sano M. Treatment of Alzheimer's disease. New Engl J Med 1999;341:1670–1679
5. Lieberman J, Pollack S, Lesser M, et al. Pharmacologic characterization of tardive dyskinesia. J Clin Psychopharmacol 1988;8:254–260
6. Ingram NAW, Newgreen DB. The use of tacrine for tardive dyskinesia. Am J Psychiatry 1983;140:1629–1631
7. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
8. Tracy K, Adler LA, Rotrosen J, et al. Interrater reliability issues in multicenter trials, pt 1: theoretical concepts and operational procedures used in Department of Veterans Affairs Cooperative Study #394. Psychopharmacol Bull 1997;33:53–57

Stanley N. Caroff, M.D.
E. Cabrina Campbell, M.D.
Joan C. Havey, B.S.
Kenneth A. Sullivan, Ph.D.
Ira R. Katz, M.D., Ph.D.
Stephan C. Mann, M.D.
Department of Veterans Affairs Medical Center and the
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Addition of Risperidone to Clozapine Therapy in Chronically Psychotic Inpatients

Sir: Patients with schizophrenia who remain severely psychotic despite several courses of treatment with classical antipsychotics and clozapine constitute a major problem in clinical practice. One 4-week open trial, reported by Henderson and Goff,[1] showed that augmentation of clozapine with risperidone produced at least a 20% reduction on the Brief Psychiatric Rating Scale (BPRS) in 10 of 12 schizophrenic outpatients with persistent psychotic symptoms.

We performed a 4-week open trial to determine the effect that the addition of risperidone to clozapine therapy would have on schizophrenic inpatients who showed persistent severely psychotic symptoms. Twelve patients (9 men and 3 women)

participated. The mean ± SD age was 41.7 ± 10.7 years, the mean duration of hospitalization was 8.1 ± 8.8 years, and the mean Positive and Negative Syndrome Scale (PANSS) score was 81.6 ± 12.9. All patients had had therapeutic serum clozapine levels for a minimum of 6 months. We started by adding 1 mg of risperidone and increased this amount gradually, on the basis of clinical response, to a maximum of 6 mg of risperidone (mean dose of risperidone at day 28 was 5.3 ± 1.4 mg). The dosage of clozapine remained unchanged for 8 weeks before the trial and during the 4 weeks of the trial. All other medication remained unchanged during the trial.

In general, the addition of risperidone to clozapine was well tolerated. One patient dropped out because of orthostatic hypotension. No changes were seen in extrapyramidal symptoms or laboratory parameters (leukocytes and differentiation). For 10 patients, the serum clozapine levels were available on 3 days, 1 before and 2 during the trial. There was a nonsignificant variation in serum concentration from 377.2 ± 129.0 µg/L (before) to 354.7 ± 129.8 µg/L (day 7) and to 355.1 ± 97.0 µg/L (day 28).

A responder was defined as a patient having a more than 20% reduction in PANSS score. None of the 11 patients was a responder on the PANSS total scale or the positive or negative subscales. Our findings suggest that adding risperidone to clozapine therapy is not an effective strategy for treating schizophrenic inpatients who have chronic and severe psychosis.

Our results therefore contradict the results reported by Henderson and Goff.[1] A possible explanation may be that their population was less severely disturbed, as is suggested by the mean BPRS score and the outpatient status. Another explanation could be that small open trials are prone to false positive or negative results.

REFERENCE

1. Henderson DC, Goff DC. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. J Clin Psychiatry 1996;57:395–397

Izaäk W. de Groot, M.Sc.
Adolph H. Heck, M.D.
Peter N. van Harten, M.D., Ph.D.
Psychiatric Center Zon & Schild
Amersfoort, the Netherlands

Antidepressant Treatment and Global Tests of Coagulation and Fibrinolysis

Sir: Although rare, an increased tendency for bleeding has been associated with various antidepressants, causing justifiable concern.[1] Knowledge about the mechanisms underlying this phenomenon is scarce.[2,3] The phenomenon is believed to represent interactions of drugs with other drugs[4,5] or with the serotonergic system of platelets.[1] Furthermore, there is some evidence that depressive disorders by themselves may affect hemostatic function.[6] To further our understanding of the clotting cascade during antidepressant treatment, we analyzed global tests of coagulation and fibrinolysis before and after treatment with either amitriptyline, a tricyclic compound, or paroxetine, which is characterized predominantly by its mode of action, namely selective serotonin reuptake inhibition.

Our study group comprised 15 female and 10 male patients (mean ± SD age = 50.2 ± 16.6 years) who had an episode of major depression according to DSM-IV and a Hamilton Rating Scale for Depression (HAM-D) score greater than 18 after 6 days of placebo. Subjects received a standardized antidepres-

sant treatment with either amitriptyline, 150 mg/day (N = 12), or paroxetine, 40 mg/day (N = 13), for a period of 35 days. The treatment groups did not differ in terms of age, gender, or severity of depression. One day before start of treatment and on day 35, citrated blood specimens were collected and were immediately centrifuged at 4°C and stored at –80°C for later analysis of fibrin-monomer-antigen (FMA), von Willebrand factor (vWF), prothrombin ratio (Quick), activated partial thromboplastin time (aPTT), and fibrinogen. Because this study focused on tests of the coagulation system, information about platelet or vessel dysfunction, such as represented in the bleeding time, was not collected. Repeated measurement analysis of variance (ANOVA) with paroxetine versus amitriptyline ("medication") as between-treatment factor and the change of parameter during "treatment" as within-treatment factor was used for analysis. None of the subjects had taken substances intervening with coagulation or platelet function during the last 4 weeks prior to enrollment, and no clinically obvious signs of an increased bleeding tendency had been observed.

There was a significant decline in HAM-D scores from day 0 to day 35 (mean ± SD pretreatment score = 23.4 ± 4.7, posttreatment score = 8.9 ± 5.7; F = 114.6, df = 1,23; p < .001), which was similar in both treatment groups. Also in both groups, ANOVA found prothrombin ratio (Quick) to increase from start to end of treatment (F = 13.7, df = 1,23; p < .002; paroxetine: mean pretreatment ratio = 94.4% ± 9.5%, posttreatment ratio = 99.1% ± 11.4%; amitriptyline: mean pretreatment ratio = 93.5% ± 12.4%, posttreatment ratio = 100.9% ± 11.0%). There was no effect of "treatment" or a "treatment medication interaction" on FMA, vWF, aPTT, or fibrinogen (all F values < 3.9).

In closing, the tests of blood coagulation and fibrinolysis we used provided no evidence of clinically relevant changes during antidepressant treatment with either amitriptyline or paroxetine. The noted increase in prothrombin ratio might be due to nutritional factors. We thus conclude that complications due to an increased tendency for bleeding that are associated with these drugs are probably not extreme forms of a general influence on the coagulation system but an idiosyncratic reaction.

REFERENCES

1. Skop BP, Brown TM. Potential vascular and bleeding complications of treatment with selective serotonin reuptake inhibitors. Psychosomatics 1996;37:12–16
2. Berk M, Jacobson BF, Hurly E. Fluoxetine and hemostatic function: a pilot study. J Clin Psychiatry 1995;56:14–16
3. Bondurant T, Darrell MJ, Asyouty SE, et al. Effect of fluoxetine on prothrombin time. Psychosomatics 1998;39:296–297
4. Apseloff G, Wilner KD, Gerber N, et al. Effect of sertraline on protein binding of warfarin. Clin Pharmacokinet 1997;32(suppl 1):37–42
5. Hampel H, Berger C, Kuss HJ, et al. Unstable anticoagulation in the course of amitriptyline treatment. Pharmacopsychiatry 1996;29:33–37
6. Musselman DL, Tomer A, Manatunga AK, et al. Exaggerated platelet reactivity in major depression. Am J Psychiatry 1996;153:1313–1317

Florian Lederbogen, M.D.
Bettina Weber, M.D.
Michael Colla, M.D.
Isabella Heuser, M.D.
Michael Deuschle, M.D.
Central Institute of Mental Health
Mannheim, Germany
Carl-Erik Dempfle, M.D.
University of Heidelberg
Mannheim, Germany