experienced some depressive symptoms not meeting the criteria for major depression. She was initially prescribed a monoamine oxidase inhibitor, but didn't want to take the tablets because she feared adverse reactions. As an alternative she was prescribed bupropion. This was increased to 300 mg/day over several days. The patient reported the onset of improvement by the 4th day.

The patient's symptoms rapidly decreased and disappeared over the next few weeks. She reported feeling quite happy and, as a result, she has become more assertive. Side effects included a loss of 5 pounds over 1 month and constipation, for which she took a laxative.

Bupropion is believed to have dopamine agonist properties.[2] Evidence suggests that dopamine interacts with GABAergic pathways in the mediation of antianxiety response. It has been reported that the cerebrospinal fluid levels of dopamine are directly correlated with extroversion as measured by the Eysenck personality inventory.[3] This may explain why monoamine oxidase inhibitors that affect adrenergic, serotonergic, and dopaminergic pathways are effective in social phobia, whereas tricyclics that affect predominantly noradrenergic and serotonergic systems may lack efficacy in relieving social phobia symptoms.[4] Buproprion may serve as a useful alternative for the treatment of social phobia. Clearly further study is warranted.

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Disseminated Intravascular Coagulation and Acute Myoglobinuric Renal Failure: A Consequence of the Serotonergic Syndrome

Editors:

Recent reports support the validity of the serotonergic syndrome in humans.[1,2] The complete syndrome may include flushing, diaphoresis, lethargy or hyperactivity, hyperreflexia, myoclonus, autonomic dysregulation, hyperthermia, hypertonicity, tremor, rigor, and disorientation. Patients' symptoms are strikingly similar to the cluster of symptoms described in the animal pharmacological literature when 5-hydroxytryptamine precursors are administered to animals pretreated with drugs that increase 5-hydroxytryptamine availability in the central nervous system.[3,4] At present, monoamine oxidase inhibitor (MAOI)-fluoxetine, MAOI-tryptophan, MAOI-tricyclic antidepressant, and MAOI-meperidine combinations have been linked with the development of the syndrome.[2,5,6] We report a case in which the serotonergic syndrome resulted in hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, and myoglobinuric renal failure.

An 18-year-old woman was hospitalized with symptoms of agitation, dysphoria, insomnia, guilty ruminations, suicidal ideation, and self-mutilation. Having been treated with fluoxetine 40 mg orally every day for 35 days without benefit, the patient was started on tranylcypromine after the fluoxetine had been discontinued for 24 days. She received tranylcypromine 10 mg orally on day 1, 20 mg orally on day 2, and 30 mg orally on day 3. At 7:45 p.m. on day 3, the patient was noted to be lethargic. By 9:00 p.m. the patient was disoriented, restless, markedly flushed, diaphoretic, and tremulous. She was shivering and exhibiting myoclonic jerks. Her pulse was 140; her blood pressure was 140/90 mm Hg; and she was afebrile (36.7°C). Her pupils were dilated, and bilateral ankle clonus and hyperreflexia were elicited. The patient was transferred to the medical intensive care unit, where she remained for 7 days. A description of the patient's vital signs and selected biochemical and hematologic values for this period are in Table 1.

On day 4 the patient's temperature increased to 42.1°C (107.8°F). She was acidotic (arterial blood gas pH, 7.25), and her creatine phosphokinase was 9520 IU/liter. Urinalysis revealed proteinuria (100 mg/dl) and gross hematuria. Cultures of blood, urine, and cerebrospinal fluid were obtained, and the patient was started on a regimen of antibiotics. The patient was intubated, placed on mechanical ventilation, and placed on a cooling blanket. Blood pressure was monitored with a central arterial line. Lumbar puncture revealed two red blood cells, two white blood cells, glucose 152 mg/dl, and protein 40 mg/dl. Acidosis was treated with sodium bicarbonate.

On day 5, the patient became hypotensive and dopamine hydrochloride therapy was instituted. Platelet consumption became apparent (Table 1), and coagulation studies revealed a protime of 23.4 seconds (control, 11 seconds), an activated partial thromboplastin time of 61.6 seconds (control, 22 seconds), fibrinogen of 95 mg/dl (normal range, 150–400 mg/dl), fibrinogen degradation products >40 mg/dl (normal, <10 mg/dl), thrombin time of 34.3 seconds (normal range, 18–25 seconds), factor V 12% (normal range, 70–120%) and factor VII 19% (normal range, 70–120%). The diagnosis of disseminated intravascular coagulation was made on the basis of these findings.

Also on day 5, the patient's urine output decreased dramatically. Myoglobinuria was diagnosed and creatinine rose from 0.7 mg/dl to 1.8 mg/dl. Intravenous Mannitol 6.25 g was administered, followed several hours later by an additional 12.5 g.

TABLE 1. Vital signs and selected biochemical courses

	Baseline	Day 3[a]		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9	Day 10
	a.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	a.m.
Temperature (°C)	37.0	37.2	39.2	42.1	41.0	39.1	38.2	38.0	37.8	38.2	38.2	37.6	37.0	37.0	37.0
Pulse (beats/minute)	66	–	160	156	178	177	138	122	123	118	114	88	–	88	80
Respirations/minute	12	–	28	32	40	27	25	12	12	12	18	–	–	–	–
Blood pressure (mm Hg)	110/70	–	150/50	142/50	128/40	106/A[b]	114/A	147/A	123/A	121/A	128/A	122/64	–	120/60	118/70
Blood gas (pH)	–	–	7.31	7.25	7.30	7.37	7.28	7.45	7.43	–	7.48	7.43	–	–	–
Hemoglobin (g/dl)	13.4	–	12.8	10.9	–	–	11.3	9.7	8.8	8.5	8.1	8.0	–	8.8	8.5
Platelets × 10^3	294	–	299	256	–	190	100	56	58	58	65	75	–	141	268
Prothrombin time (control, 11–14 seconds)	–	–	–	11.9	–	23.4	20.1	15.9	13.5	13.6	12.0	–	–	11.1	11.5
Activated partial thromboplastin time (control, 22–36 seconds)	–	–	–	21.5	–	61.6	42.1	39.3	34.0	32.8	31.6	–	–	29.8	25.2
Creatine phosphokinase (IU/liter)	32	–	563	9520	28560	31125	–	16890	13040	9640	5990	–	–	2862	–
Fibrinogen (mg/dl)	–	–	–	–	–	95	100	128	158	287	375	–	415	–	450

[a]Day 3 was the third day of tranylcypromine treatment.
[b]A, central arterial line.

A brisk diuresis ensued. Over the next 24 hours, the patient received sodium bicarbonate, calcium gluconate, magnesium sulfate, vitamin K, platelets, and fresh frozen plasma.

Although the patient's hemoglobin continued to decrease to a low of 8.0 g/dl on day 8, by that date she was extubated, her vital signs were stable, platelet consumption had abated, and protime and activated partial thromboplastin time had improved. CPK and creatinine declined, and fibrinogen increased.

The patient's neurologic status steadily improved, and by day 8 she was alert and oriented with no residual neurologic deficits. End-organ damage was indicated in the liver by an SGOT of 1580 IU/liter and an SGPT of 1740 IU/liter, in the kidney by a creatinine of 1.8 mg/dl, and in the lungs by chest X-rays showing patchy infiltration and effusions. By day 10, chest X-rays were unremarkable, SGOT was 100 IU/liter, SGPT was 372 IU/liter, and creatinine had declined to 1.1 mg/dl. All bacteriologic, fungal, and viral studies showed no growth or were negative.

Our patient's reaction to tranylcypromine 60 mg 24 days after being treated with fluoxetine is strikingly similar to the severe reactions seen in malignant hyperthermia of anesthesia, the neuroleptic malignant syndrome (NMS), and MAOI-tryptophan combinations. Brennan and colleagues[7] suggest that all of these syndromes share a final common pathway, even though dopamine blockade appears to be central in NMS, and serotonin agonism appears to be central in MAOI-tryptophan and MAOI-fluoxetine reactions.[7]

In our patient, we conclude that the serotonergic syndrome produced hyperthermia, hypertonicity, myoclonus, and rigor, which, in turn, gave rise to rhabdomyolysis, respiratory compromise, and acidosis, culminating in disseminated intravascular coagulation and myoglobinuric renal failure. The recognition of this sequence allows treatments which can interrupt the cascade of events leading to disseminated intravascular coagulation and end-organ failure.

Dantrolene sodium has been used to treat malignant hyperthermia of anesthesia, NMS, heat stroke, and MAOI overdose complicated by hyperpyrexia, muscle rigidity, and tremor.[8-12] Dantrolene sodium appears to relax the skeletal muscle directly by inhibiting calcium flux in muscle sarcoplasmic reticulum.[9] Kaplan and coauthors[8] reported that 30 minutes after administering dantrolene sodium 2.5 mg/kg intravenously, their patient, who had taken an overdose of phenelzine, experienced a dramatic resolution of muscle rigidity and hyperthermia. Our patient did not receive dantrolene, but had she, she might have been spared rhabdomyolysis and disseminated intravascular coagulation.

While treatment of hyperthermia and prevention of rhabdomyolysis are essential in averting disseminated intravascular coagulation, supportive measures to counteract hypotension, acidosis, and renal failure can be lifesaving. Accordingly, intravenous hydration, mechanical ventilation, osmotic diuretics, and vasopressors may be required.

The correct treatment of disseminated intravascular coagulation remains controversial. Our patient received platelet transfusions and factor replacement with fresh frozen plasma. While many authorities advocate the use of fresh frozen plasma, Bick,[13] in his comprehensive review, cautions that fresh frozen plasma may contribute clotting factors to fuel ongoing thrombosis and end-organ damage. Other modalities such as subcutaneous or intravenous heparin or infusion of antithrombin III could have been considered. Our patient's clinical course did not mandate more aggressive treatment.

We believe that the serotonin syndrome and its complications will be encountered increasingly in clinical practice as serotonin reuptake inhibitors gain widespread acceptance and are combined with lithium, MAOIs, tricyclic antidepressants, and te-

tracyclics when attempting to treat refractory and partially treated depression.

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Sodium-Calcium Exchange and Lithium Action

Editors:

We have read with great interest the paper of El-Mallakh and Jaziri.[1] They postulate that lithium may exert its potent antimanic effect by inhibiting Ca uptake and increasing Ca extrusion through a sodium-calcium (Na-Ca) exchange system, both actions as direct consequences of displacement of Na by lithium in the cells.

In the last few years our group has been investigating the effect of lithium on catecholamine release from the perfused cat adrenal gland,[2] a widely used experimental model for the study of the secretory process from central and peripheral catecholaminergic neuronal cells.[3] Catecholamine release from chromaffin cells is a Ca-dependent event, the extracellular medium being the principal source of calcium for the majority of stimuli.[3] Our main finding was that high concentrations of lithium (25–119 mM) enhanced the rate of catecholamine release in a time- and concentration-dependent manner, the secretion being strictly dependent on $[Ca]_o$.[2] Such a secretory profile was essentially identical to that obtained by ouabain in the same model.[4,5] Cardiac glycosides are known to inhibit the Na pump, resulting in Na accumulation in the cells and Ca entry through Na_i-Ca_o exchange in a number of tissues.[4–7] Lithium easily accumulates in the cells because it is a poor substrate for the Na-K ATPase,[8] thus leading to an ionic distribution similar, in a sense, to that obtained by inhibition of the Na pump by ouabain, the only difference being that the prevalent intracellular monovalent cation in this case is lithium instead of Na. On these grounds, we first postulated[2] that lithium could promote catecholamine release by substituting Na in the Na-Ca exchange counter transport system, thus converting the physiologic Na_i-Ca_o exchange into an artificial Li_i-Ca_o exchange. Even though some controversies exist about the ability of lithium to substitute for Na in the Na-Ca exchange system in some experimental models, Nishimura and Sorimachi[9] have demonstrated in bovine chromaffin cells that lithium can partially maintain the Na-dependent Ca efflux in the absence of Na, a finding that strongly supports our hypothesis.

Additional experiments from our laboratory have shown that organic Ca antagonists of the dihydropyridine type partially block the secretion induced by both ouabain[10] and lithium.[11] Because dihydropyridines have shown a high degree of selectivity for blocking voltage-operated Ca channels in adrenal medulla,[12] a dual mechanism was finally postulated: lithium, as ouabain, would promote catecholamine release from the cat adrenal gland (1) by depolarizing cell membrane and opening voltage-sensitive Ca channels, and (2) by activating a Li_i-Ca_o exchange (Na_i-Ca_o in the case of ouabain), both effects being a consequence of cation accumulation (lithium or Na respectively) because of the incompetence of Na-K ATPase.

Obviously, our results cannot be extrapolated to other neuronal tissues nor to human beings, even less to explain the mechanism of therapeutic action of lithium in affective disorders. However, they suggest that if lithium accumulates sufficiently in cells to displace the intracellular Na, as El-Mallakh and Jaziri postulate, a promoting effect instead of a blocking effect on Ca entry would take place. At therapeutic lithium plasma levels, such a catecholamine secretory effect probably does not occur, and other more sensitive intracellular systems may play a major role in the mechanism of antimanic action of lithium.[13,14]

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