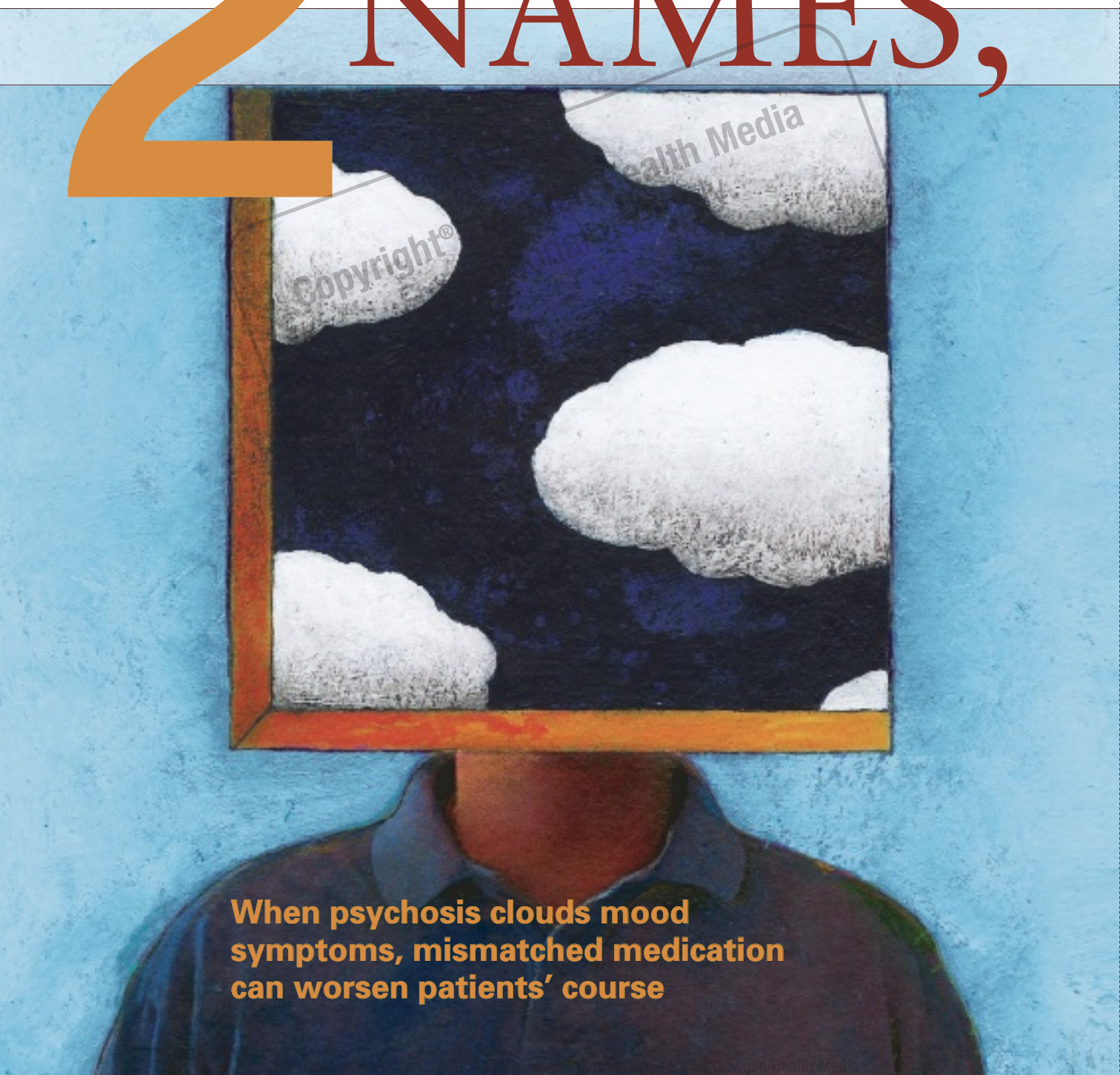
2 NAMES,



When psychosis clouds mood symptoms, mismatched medication can worsen patients' course

Current PSYCHIATRY

1 DISEASE

Does schizophrenia = psychotic bipolar disorder?

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When a patient presents with psychotic symptoms, you might not recognize or pursue hints of bipolarity if you assume psychosis means schizophrenia. Yet psychotic bipolar disorder can explain every sign, symptom, course, and other characteristic traditionally assumed to indicate schizophrenia (*Table 1, page 44*). The literature, including recent genetic data,[1-6] marshals a persuasive argument that patients diagnosed with schizophrenia usually suffer from a psychotic bipolar disorder.

Consider here how a cascade of changing signs and symptoms, initially unrecognized, caused five sequential re-evaluations of one psychotic patient's primary Axis I diagnosis. His case highlights why the correct initial diagnosis of the disease causing psychosis is essential to effective treatment.[4,7-9]

CASE: CARVED IN STONE

Police officers carry Mr. C, age 30, into the emergency department (ED). He is mentally disorganized and arrives in a rigid, catatonic posture. According to a neighbor, Mr. C was kneeling motionless on his

Table 1

DSM-IV-TR criteria for schizophrenia vs. psychotic mood disorder

Schizophrenia diagnosis[6]	Seen in psychotic mood disorders
Criterion A	
Hallucinations and delusions	50% to 80% explained by mood[16,21]
Paranoia	Hides grandiosity[4]
Catatonia	75% explained by mood[7,8]
Disorganized speech and behavior	All patients with moderate to severe mania[1-5]
Negative symptoms	All patients with moderate to severe depression[4]
Criterion B	
Social and job dysfunction	All patients with moderate to severe bipolar disorder[5,13]
Criterion C	
Chronic continuous symptoms	Patients can have psychotic symptoms continuously for 2 years to life[5,6,13]

mother's front lawn, alternating between mutism and inappropriately loud, disorganized religious preaching. When his arm is lifted, it remains as placed. He is admitted to the acute care inpatient unit.

Mr. C's most striking symptoms are catatonia and psychosis. Postural rigidity, waxy flexibility, and automatic obedience are characteristics of catatonia.[6-8] An organic cause is first considered, such as hyperthyroidism, cerebrovascular accident, cerebral neoplasm, head trauma, seizure disorder, dementia, neuroleptic malignant syndrome, pheochromocytoma, or—especially—intoxication from illegal drugs.[7]

While awaiting results from physical, mental status, and lab exams and imaging studies, staff assign him two admitting diagnoses: catatonic disorder due to a general medical condition and psychotic disorder not otherwise specified.[6]

CASE: INCONCLUSIVE WORKUP

Mr. C denies using illegal substances or alcohol, which his mother confirms. He has no history of seizures or other medical conditions. His distractibility prevents him from focusing on a formal mental status exam. Physical exam, urine drug screen, lab results, and imaging studies are unremarkable except for an admitting blood pressure of 145/95 mm Hg and pulse of 115 beats per minute. These readings normalize within 1 hour. IM haloperidol and lorazepam are given as needed for agitation, but physicians withhold scheduled medications to allow staff to observe his symptoms.

Organic causes of catatonia now seem less likely, though past use of drugs such as phencyclidine that can cause chronic psychosis cannot be ruled out. Schizophrenia is considered likely because catatonia is one of schizophrenia's five core diagnostic symptoms.[6] Catatonia can also be a symptom of bipolar disorder.[6-9] Staff make a preliminary diagnosis of schizophrenia, catatonic type.

CASE: 'HIT MEN ARE AFTER ME'

Staff observe Mr. C responding to threatening auditory hallucinations. His affect is "fearful to terrified." He

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Continued brief summary of prescribing information from previous page.

Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules

Adverse Events in Clinical Studies with Focalin™ XR – Adults

Adverse Events Associated with Discontinuation of Treatment: In the adult placebo-controlled study, 10.7% of the Focalin XR-treated patients and 7.5% of the placebo-treated patients discontinued for adverse events. Among Focalin XR-treated patients, insomnia (1.8%, n=3), feeling jittery (1.8%, n=3), anorexia (1.2%, n=2), and anxiety (1.2%, n=2) were the reasons for discontinuation reported by more than 1 patient.

Adverse Events Occurring at an Incidence of 5% or More Among Focalin™ XR-Treated Patients: Table 2 enumerates treatment-emergent adverse events for the placebo-controlled, parallel-group study in adults with ADHD at fixed Focalin XR doses of 20, 30, and 40 mg/day. The table includes only those events that occurred in 5% or more of patients in a Focalin XR dose group and for which the incidences in patients treated with Focalin XR appeared to increase with dose. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 2
Treatment-Emergent Adverse Events[1] Occurring During Double-Blind Treatment – Adults

	Focalin™ XR 20 mg N=57	Focalin™ XR 30 mg N=54	Focalin™ XR 40 mg N=54	Placebo N=53
No. of Patients with AEs				
Total	84%	94%	85%	68%
Primary System Organ Class/ Adverse Event Preferred Term				
Gastrointestinal Disorders	28%	32%	44%	19%
Dry Mouth	7%	20%	20%	4%
Dyspepsia	5%	9%	9%	2%
Nervous System Disorders	37%	39%	50%	28%
Headache	26%	30%	39%	19%
Psychiatric Disorders	40%	43%	46%	30%
Anxiety	5%	11%	11%	2%
Respiratory, Thoracic and Mediastinal Disorders	16%	9%	15%	8%
Pharyngolaryngeal Pain	4%	4%	7%	2%

[1]Events, regardless of causality, for which the incidence was at least 5% in a Focalin XR group and which appeared to increase with randomized dose. Incidence has been rounded to the nearest whole number.

Two other adverse reactions occurring in clinical trials with Focalin XR at a frequency greater than placebo, but which were not dose related were: Feeling jittery (12% and 2%, respectively) and Dizziness (6% and 2%, respectively).

Table 3 summarizes changes in vital signs and weight that were recorded in the adult study (N=218) of Focalin XR in the treatment of ADHD.

Table 3
Changes (Mean ± SD) in Vital Signs and Weight by Randomized Dose During Double-Blind Treatment – Adults

	Focalin™ XR 20 mg N=57	Focalin™ XR 30 mg N=54	Focalin™ XR 40 mg N=54	Placebo N=53
Pulse (bpm)	3.1 ± 11.1	4.3 ± 11.7	6.0 ± 10.1	-1.4 ± 9.3
Diastolic BP (mmHg)	-0.2 ± 8.2	1.2 ± 8.9	2.1 ± 8.0	0.3 ± 7.8
Weight (kg)	-1.4 ± 2.0	-1.2 ± 1.9	-1.7 ± 2.3	-0.1 ± 3.9

Adverse Events with Other Methylphenidate HCl Dosage Forms

Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed below may also occur.

Other reactions include: ***Cardiac:*** angina, arrhythmia, palpitations, pulse increased or decreased, tachycardia; ***Gastrointestinal:*** abdominal pain, nausea; ***Immune:*** hypersensitivity reactions including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura; ***Metabolism/Nutrition:*** anorexia, weight loss during prolonged therapy; ***Nervous System:*** dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette's syndrome, toxic psychosis; ***Vascular:*** blood pressure increased or decreased, cerebral arteritis and/or occlusion

Although a definite causal relationship has not been established, the following have been reported in patients taking methylphenidate: ***Blood/Lymphatic:*** leukopenia and/or anemia; ***Hepatobiliary:*** abnormal liver function, ranging from transaminase elevation to hepatic coma; ***Psychiatric:*** transient depressed mood, aggressive behavior; ***Skin/Subcutaneous:*** scalp hair loss

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules, like other methylphenidate products, is classified as a Schedule II controlled substance by Federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Poison Control Center

The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

Recommended Treatment

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

When treating overdose, practitioners should bear in mind that there is a prolonged release of dexmethylphenidate from Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules.

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis for Focalin overdosage has not been established.

Store at 25°C (77°F), excursions permitted 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]

Dispense in tight container (USP).

Focalin™ XR is a trademark of Novartis AG
SODAS® is a trademark of Elan Corporation, plc.

This product is covered by US patents including 5,837,284, 5,908,850, 6,228,398, 6,355,656, and 6,635,284.

REFERENCE

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association 1994.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
By ELAN HOLDINGS INC.
Pharmaceutical Division
Gainesville, GA 30504

continued from page 44

says he hears the voice of God warning him of danger and continuing a running commentary on his actions. He fears for his life because "hit men have been sent to kill me" and have "infiltrated" the inpatient ward. He does not eat, saying his food is poisoned. He says these beliefs have escalated over the past year.

Mr. C's catatonic symptoms resolve overnight, but obtaining additional history is difficult because of his paranoia. He denies any history of bizarre behavior or past contact with mental health services. He claims not to be especially religious. He is unmarried and lives with his mother, is college-educated, but has held only menial jobs.

> Mr. C says God's voice is warning him that 'hit men' have 'infiltrated' the inpatient ward

Inpatient staff shifts its diagnostic focus to functional disorders associated with auditory hallucinations, paranoid delusions, and gross disorganization. According to Schneider and the DSM-IV-TR,[6,10] hearing a voice "keeping up a running commentary on one's behavior" is especially diagnostic of schizophrenia.

Because of the rapid resolution of his "catatonic" symptoms and prominence of paranoia, they change his diagnosis on day 2 to schizophrenia, paranoid type. Mr. C meets all diagnostic criteria for schizophrenia except one: the staff has overlooked and has not adequately excluded a psychotic mood disorder.

CASE: A TURN FOR THE WORSE

That night, nursing staff find Mr. C naked and cowering in the fetal position in a corner of his room. He has

smeared his feces on his face and in his hair and mouth. While being cleaned up, he suddenly begins quoting scripture in a loud, disorganized voice. His expressed thoughts are incomprehensible. He is given haloperidol and lorazepam immediately; oral haloperidol is continued at 10 mg bid.

Both Bleuler and Kraepelin concluded "coprophilia and coprophagia are unique to children and patients with schizophrenia."[11,12] The DSM casebook cites Kraepelin's description of a catatonic patient who "smeared feces about" as a "classic, textbook case" of schizophrenia.[11] The casebook goes on to say: "In the absence of any known general medical condition, the combination of coprophilia, disorganized speech, and catatonic behavior clearly indicates the diagnosis of schizophrenia."

Mr. C shows each of these. Staff changes his diagnosis again—to schizophrenia, disorganized type, which carries a poor prognosis.[11,12]

Mr. C has grandiosity, lack of need to sleep, racing thoughts, hallucinations, and delusions

CASE: BANKING AND RAY GUNS

By day 5, Mr. C's mental status is normalizing and his psychosis improving. He volunteers for a weekly student case conference. There, he reveals additional information that staff could have discovered at admission with more-focused questions.

He reports that 2 years earlier he suffered severe suicidal depression. Six months later, during a hypomanic episode, he began "toying with the idea" that he might become part owner of his local bank. He believes "the Secret Service decided to transfer ownership to me."

His plans upon acquiring the bank include buying three houses and six cars valued at several million dollars and running for state governor. For weeks before admission, he did not need sleep, experienced an increase in energy and activities, and his mind was racing. His job seemed so "trivial" that he quit. Immediately before his hospital admission, his delusions intensified to include an "evil conspiracy" to murder him for ownership of the bank and he feared his execution was imminent.

He explains his catatonic behavior on the lawn by his belief that "hit men" hiding across the street aimed a "motion-detecting, heat-seeking ray gun" at him so that if he had "moved an inch," he would die. He says the "feces incident" was an effort to get himself transferred to the state hospital, where he thought he would be safer because his present caretakers were "infiltrated." He also says his mother received electroconvulsive therapy in her 20s.

These symptoms—especially the striking grandiosity, lack of need for sleep, racing thoughts, hallucinations and delusions—define a manic episode with psychotic features. Only one manic episode as described here is diagnostic of bipolar disorder, type I.[2,6,13] Staff changes his diagnosis to schizoaffective disorder, a compromise used to include patients with bipolar and psychotic (schizophrenic) features. Some authors contend schizoaffective disorder is psychotic bipolar disorder and not a separate disease.[3,4,9]

CASE: FROM SSRI TO LITHIUM

After 2 weeks, Mr. C is discharged on haloperidol, 5 mg bid, but no mood stabilizer. He receives follow-up care at a community mental health center. When he develops severe depressive symptoms 6 months after discharge, the attending psychiatrist starts him on a selective serotonin reuptake inhibitor (SSRI). Within 2 weeks, Mr. C switches from depression to a mixed, dysphoric mania. After the SSRI is discontinued and lithium is added to his haloperidol, his mood gradually stabilizes to moderate depression. He develops rigidity, masked faces, and a fine tremor in his hands.

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nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence, and asthenia). ***Male and Female Sexual Dysfunction with SSRIs:*** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labelling are likely to underestimate their actual incidence. In placebo-controlled clinical trials involving more than 1,800 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, and panic disorder are displayed in Table 4. **Table 4. Incidence of Sexual Adverse Events in Controlled Clinical Trials (in males only: paroxetine: n=925; placebo: n=655):** decreased libido (6% - 14% vs. 0% - 5%), ejaculatory disturbance (13% - 28% vs. 0% - 1%), impotence (2% - 8% vs. 0% - 1%); **(in females only: paroxetine: n=932; placebo: n=694):** decreased libido (1% - 9% vs. 0% - 2%), orgasmic disturbance (2% - 9% vs. 0% - 1%). There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment. Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. ***Weight and Vital Sign Changes:*** Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss vs. smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with paroxetine in controlled clinical trials. **Other Events Observed During the Premarketing Evaluation of Paroxetine:** During its premarketing assessment in major depressive disorder, multiple doses of paroxetine were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to paroxetine varied greatly and included (in overlapping categories) open and double blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. During premarketing clinical trials in OCD and panic disorder, 542 and 469 patients, respectively, received multiple doses of paroxetine. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of paroxetine who experienced an event of the type cited on at least one occasion while receiving paroxetine. All reported events are included except those already listed in Tables 1 and 2, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. ***Body as a Whole:*** *infrequent:* allergic reaction, chills, face edema, malaise, neck pain; *rare:* adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer. ***Cardiovascular System:*** *frequent:* hypertension, tachycardia; *infrequent:* bradycardia, hematoma, hypotension, migraine, syncope; *rare:* angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. ***Digestive System:*** *infrequent:* bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, chlolelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries. ***Endocrine System:*** *rare:* diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis. ***Hemic and Lymphatic Systems:*** *infrequent:* anemia, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia. ***Metabolic and Nutritional:*** *frequent:* weight gain; *infrequent:* edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. ***Musculoskeletal System:*** *frequent:* arthralgia; *infrequent:* arthritis, arthrosis; *rare:* bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany. ***Nervous System:*** *frequent:* emotional lability, vertigo; *infrequent:* abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome. ***Respiratory System:*** *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration. ***Skin and Appendages:*** *frequent:* pruritus; *infrequent:* acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. ***Special Senses:*** *frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia ptosis, retinal hemorrhage, taste loss, visual field defect. ***Urogenital System:*** *infrequent:* amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, pyuria, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis. **Postmarketing Reports:** Voluntary reports of adverse events in patients taking paroxetine that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide, tremor and trismus; serotonin syndrome, associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired paroxetine metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of paroxetine and phenytoin co-administration. There has been a case report of severe hypotension when paroxetine was added to chronic metoprolol treatment.

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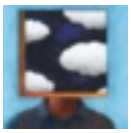

Psychosis

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About 10% of bipolar depressed patients given an antidepressant—especially without a mood stabilizer—switch to mania, and their cycle frequency increases.[2,13-15] A correct initial diagnosis and treatment with a mood stabilizer might have avoided Mr. C's switch.

Mixed bipolar disorder with overlapping depressive and manic symptoms is often resistant to monotherapy, requiring two or more mood stabilizers such as lithium and an anticonvulsant.[14] Without a mood-stabilizing combination, the mixed, rapid-cycling type of bipolar disorder is likely to progress, with more-rapid and more-severe episodes.[2,13-15] Adding lamotrigine, a mood stabilizer with antidepressant effects, can help.[2,14]

Stopping the SSRI is correct, despite Mr. C's severe depression, to avoid increasing the cycle frequency.[13-15] Some authors recommend tapering the antipsychotic, using it only as needed for psychotic features after psychosis has resolved.[14-17] Continuing antipsychotic drugs after psychosis has remitted increases rates of cycling to depression, depressive and extrapyramidal symptoms, and medication discontinuation.[17] Lithium may have aggravated Mr. C's antipsychotic-induced parkinsonism, but discontinuing haloperidol may have been the most therapeutic decision.

The community mental health staff changes his diagnosis again, this time to bipolar disorder, type I, mixed, severe with psychotic features. We concur that this is correct.

What do you think?

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CASE: A DIAGNOSTIC STEP BACK

Two years later, Mr. C is working and continues to take lithium and haloperidol prescribed at the mental health center. His intermittent depressive episodes persist, but—apparently because he has not had another manic episode—the staff switches his diagnosis back to schizoaffective disorder.

We disagree with this change. A diagnosis of schizoaffective disorder precludes ideal pharmacotherapy for Mr. C's rapid-cycling bipolar disorder and increases the risk of adverse drug effects and stigma. Persuasive evidence shows that schizoaffective disorder is psychotic bipolar disorder; there is no schizoaffective disorder (*Box*).[3,4,16-18]

MISDIAGNOSIS OF PSYCHOSIS

Bipolar disorder can be missed when patients present with psychotic symptoms, but clinicians could have initially recognized Mr. C's bipolar disorder. His diagnostic trail illustrates important points about psychotic presentations:

- Predominant psychotic symptoms can obscure mood disturbances.
- Mistakenly believing that psychosis means schizophrenia can jeopardize patient care.
- When paranoia and fear hide grandiosity, then mania—not schizophrenia—is likely.
- Psychotic mood disorders—not schizophrenia—cause functional psychosis; there is no schizophrenia (*Box*).
- Pursuing mood symptoms in psychotic presentations is critical in an initial diagnostic interview.

Questioning the concept that hallucinations, delusions, catatonia, and disorganization are specific to and diagnostic of schizophrenia is not new. In 1978, Pope and Lipinski compared symptoms, course, outcome, family history, and responses to lithium in bipolar disorder and schizophrenia.[3] They and others find no symptom, group of symptoms, or course that differentiates schizophrenia from psychotic bipolar disorder.[3-5,8,9,16,18,19] They conclude that most cases diagnosed as schizophrenia or schizoaffective disorder are misdiagnosed cases of bipolar illness, whereas others question the validity of schizophrenia.[20]

Bipolar disorder has a broad spectrum of severity and course; it frequently reaches psychotic levels that can become chronic.[2,5,21] Psychotic symptoms of rigorously diagnosed bipolar patients can deteriorate until their overwhelming psychosis obscures bipolar symptoms.[5,6,13,21] Like most, if not all, acutely psychotic bipolar patients, Mr. C shows all diagnostic criteria for schizophrenia.[1-6,21]

Patients with severe, psychotic bipolar disorder can stop responding to medication and suffer chronic deterioration without remission.[5,21] They

Box

Schizophrenia: No such disease?

Three disorders—schizophrenia, schizoaffective disorder, and psychotic bipolar disorder—have been evoked to account for the variance in severity in psychotic patients, but psychotic bipolar disorder expresses the entire spectrum. We concur with others that psychotic bipolar disorder includes patient populations typically diagnosed as having schizophrenia and schizoaffective disorder.[3,4,9,16-18] In other words, there is no schizophrenia or schizoaffective disorder.[4,19]

Based on these data, we advocate re-evaluating all patients diagnosed with schizoaffective disorder and schizophrenia, with detailed inquiry for personal and family histories of mania or hypomania. A mood stabilizer may be warranted in some patients with psychosis but without clear manic symptoms. In such cases, we suggest using a provisional DSM-IV-TR diagnosis of psychotic disorder not otherwise specified while you seek obscure mood and/or organic causes.

Table 2

Characteristics indicating a mood disorder, not schizophrenia*

History	Past diagnosis or symptoms of a mood disorder; family history of mood disorder or alcoholism
Past medications	Lithium, valproic acid, or other mood stabilizers
Periods of uncharacteristic and excessive goal-directed activities	Political, religious, legal, sexual, business, criminal, medical, physical, spending, calling, writing, preaching, cleaning, planning, exercise
Presence of uncharacteristic emotions or conflict	Irritability, anger, violence, conflict with law enforcement, elation, grandiosity (paranoia), sadness, hopelessness, crying, suicidal ideation
Periods of appropriate affect	Smiles, laughs, cries, irritable, angry
Mood-congruent delusions and/or hallucinations	Consider grandiosity when there is paranoia and fear
Episodes of relatively normal function/remission; premorbid personality positive	Friends, dating, team sports, group activities, election to an office/title, club or gang memberships
Current social interactions	Enjoys a friendship, active interactions with spouse and own children, regular interactions with others

* Absence of any or all does not rule out mood disorder.

can lose their jobs, families, friends, and health until they are homeless, hungry, sick, and psychotic. A deteriorating course such as this has typically defined the schizophrenic process, but this concept has been reassessed.[1-6,13,15]

Most, but not all, bipolar type I patients experience psychosis. Mr. C's bipolar symptoms were not initially obvious because of predominant psychosis and were revealed only with specific, focused questions. Without the student case conference, his diagnosis might have remained schizophrenia. His treatment would have remained substandard because of the conventional belief that schizophrenia requires lifelong antipsychotics, usually without mood stabilizers.

Our patient satisfied all DSM-IV-TR criteria for both schizophrenia and psychotic bipolar. Bleuler and Schneider would have diagnosed him as having schizophrenia because they thought all psychotic disorders were schizophrenic.[10,12] They were incorrect, as psychotic symptoms are common in patients with severe bipolar disorder.[1-6,13,22]

CLINICAL IMPLICATIONS

Our observations about this case suggest four important clinical questions:

- Do data justify diagnosing patients such as Mr. C with bipolar disorder and not schizophrenia?
- Do data substantiate either diagnosis as valid?

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- Does the diagnosis matter?
- What is standard-of-care treatment for these patients?

Which diagnosis? No psychiatric disorder can be validated as rigorously as Koch's postulates did for infectious diseases. To be considered scientifically grounded, a psychiatric illness must show one or more symptoms not found in any other disorder. Bipolar disorder meets this criterion; schizophrenia does not because the psychotic symptoms and chronic course used to diagnose it are not disease-specific. Psychotic symptoms are not diagnostic of bipolar disorder but define its severity.[6]

Evidence for validity? Bipolar disorder's two extremes in mood and behavior are so different from those in persons without bipolar disorder or with any other condition that homogeneous bipolar populations can be identified and studied with confidence.[2,5,13,21] DSM-IV-TR diagnostic symptoms for bipolar disorder are unique (*Table 2, page 54*).

For a psychiatric disorder to be considered valid, patients must share other characteristics. Bipolar disorder has been validated as a specific disease by consistent genetic,[1,13,23,24] pharmacologic,[2,14,15] and epidemiologic[1] data accumulated across 30 years. The concordance for bipolar disorder in monozygotic twins is approximately 75%, and susceptibility loci for bipolar disorder are established.[23,24]

Does the diagnosis matter? Failing to make an accurate initial diagnosis can worsen the course of patients who present with psychosis (*Table 3*):

- Bipolar illness not treated with mood stabilizers progresses, with episodes becoming more frequent and severe.[2,14,15]
- Antipsychotics are given longer and in higher dosages for schizophrenia than for psychotic bipolar disorder and tend to have more common, chronic, and disabling adverse effects than do antidepressants and mood stabilizers.[14,16]
- Mr. C was given an antidepressant without mood stabilization, which is contraindicated in bipolar I disorder (especially mixed type) because the cycling rate increases.[2,14,15]

Paranoia and fear often hide grandiosity that is diagnostic of bipolar disorder, but patients such as Mr. C focus on perceived threats to their lives, not their grandiose delusions. Admitting physicians listening to their paranoid complaints may overlook the grandiose source and the possibility of psychotic bipolar disorder. Mr. C's manic grandiosity explains the motivation for each of his psychotic behaviors: paranoid delusions, catatonia, and coprophilia.

Table 3

Consequences of misdiagnosing psychotic mood disorder as schizophrenia

For patient

- Less likely to receive a mood stabilizer or antidepressant
- Without a mood stabilizer, cycles increase and occur more rapidly; symptoms worsen
- More likely to receive neuroleptics for life, increasing risk for severe and permanent side effects
- Greater stigma with schizophrenia
- Less likely to be employed
- More likely to receive disability for life
- More likely to "give up"

For clinician

- Increased risk of liability if patient given long-term neuroleptics instead of mood stabilizers develops tardive dyskinesia or commits suicide

continued

Table 4

Mr. C's symptoms that indicated bipolar disorder

Religiosity	Loud preaching and no past special interest in religion
Catatonia	Most frequently associated with bipolar disorder
Paranoia; fear	Usually hides grandiosity, which is diagnostic of mania
Distractibility	Could not stay focused in the diagnostic interview; showed 'flight of ideas'
Pressured speech	Rapid, disorganized thoughts
Disorganization	Hallmark of mania; present in all patients with severe mania
Functional psychosis	If an organic cause is ruled out, a psychotic mood disorder is the most likely diagnosis
Trouble with the law	Police found patient disturbing neighborhood and escorted him to hospital
Patient history	Severe depression
Family history	Mother was treated for depression with ECT

ECT: electroconvulsive therapy

Several initial signs could have raised suspicion that Mr. C had psychotic bipolar disorder (*Table 4*). Standard-of-care treatment in psychotic patients is predicated on early and correct diagnosis. On the basis of the evidence and our experience, we recommend that you look for bipolar symptoms when a patient:

- presents for the first time with psychosis, and you rule out an organic cause
- is readmitted for treatment of psychotic symptoms after having been diagnosed with schizophrenia.

What is standard of care? Patients with psychotic mania warrant polypharmacy:

- an antipsychotic, with or without a benzodiazepine for sedation, to enhance ward safety and treat acute psychotic symptoms
- and a first-line mood stabilizer such as valproate, carbamazepine, lithium, or lamotrigine, followed by atypical antipsychotics.

Antidepressants appear to be contraindicated, even in psychotic bipolar depressed patients.[14,15] We suggest that you taper and discontinue the initial antipsychotic when psychotic symptoms resolve. Some data indicate that continuing antipsychotics in psychotic bipolar patients is detrimental after the psychosis has resolved.[17] Medication-resistant cases may require two or three mood stabilizers and possibly an atypical antipsychotic.

The idea that "symptoms should be treated, not the diagnosis" is inaccurate and provides substandard care. When psychotic symptoms overwhelm and obscure bipolar symptoms, giving only antipsychotics is beyond standard of care.

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Bottom Line

Evidence supports the idea that functional psychoses are predominantly—if not entirely—caused by psychotic mood disorders. Misdiagnosing bipolar patients as schizophrenic and treating them with chronic antipsychotics worsens their course. Vigorously pursuing mood symptoms in patients with psychosis increases the likelihood of accurate initial diagnosis and effective treatment.

Related resources

- Berrettini WH. Molecular linkage studies of bipolar disorders. *Bipolar Disord* 2001;3:276-83.
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DRUG BRAND NAMES

Haloperidol • Haldol
Lamotrigine • Lamictal
Lithium • Lithobid
Lorazepam • Ativan
Carbamazepine • Tegretol
Valproate • Depakote

DISCLOSURE

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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