Current PSYCHIATRY

CASES THAT TEST YOUR SKILLS

Mr. F—with a history of severe motor effects and noncompliance—seems 'damned' to a life of delusional, violent behavior. After 17 years of treatment failures, can a more tolerable therapy be found?

Treating schizophrenia in the 'real world'

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HISTORY Jesus' 'cousin'

Mr. F, age 60, was hospitalized in May 1995 after expressing fear he would hurt—or kill—himself or someone else. He cooperated with admission procedures but refused to participate in ward activities or meetings. His hygiene was poor, he made little eye contact, and reportedly heard voices. Two days after admission, he emphatically denied suicidal or homicidal ideation and was discharged against medical advice.

Two weeks later, Mr. F was readmitted after his symptoms worsened. He said voices told him that he was a cousin to Jesus Christ and that he had telepathic abilities. He also reported visual hallucinations.

Twice divorced, Mr. F has three uncles who have been diagnosed with schizophrenia. His late father had a history of alcohol abuse, and his late mother suffered from Alzheimer's disease.

Mr. F lived a normal life until 1975, when he began drinking heavily. Three years later, he quit his job of 11 years at the local airport. At that time, he told a psychiatrist that "people are out to get me. I feel nervous a lot." He was diagnosed as having generalized anxiety disorder and treated with diazepam, 20 mg/d.

Four months later he complained of severe insomnia, was diagnosed with depression, and was prescribed amitriptyline, 100 mg at bedtime. He was hospitalized 1 week later after he complained of chest pain and expressed paranoid thoughts. During the 3-week hospitalization, he experienced persecutory delusions and heard voices telling him he was "damned." He was diagnosed with paranoid schizophrenia and alcohol dependence. The amitriptyline was stopped, and Mr. F was discharged on chlorpromazine, 300 mg/d.

From 1978 to 1995, Mr. F was hospitalized 35 times, often at his family's urging after he made threats or became violent at home. He once kicked his elderly father and another time was jailed after a domestic violence incident. Religious delusions characterized his thought content. Thought blocking, flight of ideas, and somatic and sexual delusions were also apparent.

continued

Was Mr. F's diagnosis accurate, or do his frequent psychotic episodes meet criteria for a type of mania?

Dr. Canive's observations

Diagnoses of mania or mood disorder with psychotic features were not considered because Mr. F never experienced a distinct period of persistently expansive or depressed mood.

Mr. F's initial complaints of increased anxiety and depression were considered prodromal symptoms of schizophrenia and may have reflected his inability to discuss or cope with his delusions and hallucinations during the initial evaluation. What's more, his occupational functioning gradually deteriorated months before his initial mental health assessment.

TREATMENT Many medications, no progress

At different times from 1978 to 1995, Mr. F had taken chlorpromazine, 100 to 300 mg/d; thioridazine, 50 to 200 mg/d; loxapine, 25 mg/d; fluphenazine, 5 to 10 mg/d; haloperidol, 2 to 4 mg/d, and fluphenazine decanoate, 3.125 to 6.25 mg biweekly, as well as concomitant anticholinergics, benzodiazepines, or other hypnotics.

A closer look at Mr. F's chart revealed that medication noncompliance often preceded hospitalization. He was extremely prone to antipsychotic-related extrapyramidal symptoms (EPS), even at low dosages. Whenever motor symptoms surfaced, he would stop taking his antipsychotics.

Buccolingual tardive dyskinesia (TD) was first noticed in 1987. Four years later, an Abnormal Involuntary Movement Scale (AIMS) exam revealed mild TD that was managed with vitamin E, 400 IU/d.

While hospitalized, Mr. F many times received injectable antipsychotics and benzodiazepines, mostly to control violence. Depot antipsychotics also were tried in an effort to promote compliance, but recurrent alcohol abuse often triggered a relapse.

How would you confront Mr. F's history of noncompliance? Can his delusions be controlled without prompting severe motor effects?

Dr. Canive's observations

For Mr. F, poor tolerability, incomplete efficacy, and variable compliance have repeatedly led to symptom exacerbation and hospitalization. Low dosing because of sensitivity to EPS may partially explain his insufficient response to antipsychotics.

In 1995, after numerous unsuccessful drug treatments, we considered entering Mr. F into a phase II clinical trial of the atypical antipsychotic aripiprazole.

Now FDA-approved for treatment of schizophrenia, aripiprazole decreases dopaminergic transmission in the nigrostriatal and tuberoinfundibular pathways, thus reducing the likelihood of EPS.[1,2] Also, aripiprazole's dopamine-serotonin stabilization effects have been reported in clinical trials to improve tolerability, compliance, and overall effectiveness in patients with schizophrenia.[3]

Common side effects of aripiprazole are mild nausea, insomnia, and restlessness, although data

Table

Mr. F's progress while taking aripiprazole, 1995-2003

Visit	CGI-S	CGI-G	PANSS Positive	PANSS Negative	PANSS total	Clinical correlates
Baseline	4	5	24	21	94	---
Week 2	3	2	N/A	N/A	N/A	Positive, negative symptoms much improved
Week 12	3	2	11	16	56	Mr. F's understanding about his illness, life, socioeconomic issues much improved
Week 76	3	2	11	18	56	Activity level increased; starts doing yard work to supplement disability income
Week 88	3	2	12	14	52	Volunteers as courier at local hospital; continues to do yard work
Week 226	2	2	9	12	42	Starts steady work as a janitor and security aid
Week 284	2	2	9	14	45	Concerned about losing Social Security benefits, since he is working 40 hours a week.
Week 328	3	1	11	15	52	Discharged from hospital after psychotic relapse. Looking for apartment.
Week 384 (Final visit)	3	1	9	12	45	Father died the previous week. Mr. F accepted his father's passing well. Open-label study terminated. Patient continued on aripiprazole, 20 mg/d.

What the scores mean

Clinical Global Impression-Severity of Illness (CGI-S)—Scores range from 1 to 7, with 1 meaning normal (normal, minimal, mild, moderate, moderately severe, severe, among the most extreme).

Clinical Global Impression-Global Improvement (CGI-G)—Scores range from 1 to 7, with 1 meaning very much improved (very much improved, much improved, improved, unchanged, little worse, much worse, very much worse).

Positive and Negative Syndrome Scale (PANSS)
Positive—consists of 7 items (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, hostility); scores range from 7 to 49 and decrease as patients improve.

PANSS Negative—consists of 7 items (blunted affect, emotional withdrawal, poor rapport, passive pathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking); scores range from 7 to 49 and decrease as patients improve.

PANSS General—consists of 16 items (somatic concern, anxiety, guilt feelings, tension, mannerism and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, active social avoidance). Scores range from 16 to 112 and decrease as patients improve.

indicate that these effects have a low prevalence and disappear within 2 weeks. If insomnia and restlessness are prominent, a low-dose, short-acting benzodiazepine may be added, tapered after 1 week, and discontinued at week 2.

CONTINUED TREATMENT A new trial

Mr. F participated in a 4-week, double-blind, placebo-controlled trial of aripiprazole, 2, 10, or 30 mg/d, versus haloperidol, 10 mg/d.

One month later, he entered a second aripiprazole trial: a 4-day, open-label study starting at 5 mg/d with titration to 20 mg/d. In the interval between the two trials, Mr. F was prescribed thiothixene, 10 mg/d, and benztropine, 2 mg at bedtime.

During the 4-day trial, he complained of insomnia and was given chloral hydrate, 500 to 1,000 mg at bedtime. He also complained of anxiety and was started on lorazepam, 2 mg bid.

After completing the open-label aripiprazole trial, Mr. F exhibited no behavioral problems and complied with ward routine. He was discharged after 17 days, at which time he denied auditory or visual hallucinations. His thinking seemed clear and his insight improved. His Global Assessment of Functioning (GAF) score at discharge was 55, suggesting moderate symptoms and difficulty in social and occupational functioning.

For the next 5 1/2 years, Mr. F was maintained on aripiprazole, 20 mg/d, as part of the same ongoing open-label trial. During that period he also took lorazepam, 1 mg bid prn; oxazepam, 15 mg bid; or clonazepam, 0.5 mg bid, for anxiety.

Mr. F. exhibited significant sustained improvement as measured with the Positive and Negative Symptom Scale (PANSS), Clinical Global Impression scale (CGI), and GAF (*Table*). His TD remained mild throughout the trial, as determined through AIMS scores. He also reported no EPS, akathisia, or other adverse events.

About 18 months after starting aripiprazole, Mr. F resumed working part time. In September 2001, he stopped receiving disability benefits and started supporting himself again.

Bottom Line

Medication noncompliance often derails schizophrenia treatment and precipitates relapse. Drug tolerability, a strong therapeutic alliance, increased social support, and cognitive-behavioral and psychosocial interventions can help promote compliance.

FOLLOW-UP 'The voices were ugly'

In December 2001, after 6 years without hospitalization, Mr. F was back in the psychiatric ward. One week before admission, he reported that he had been having panic attacks because "the voices were ugly." He only slept 4 to 5 hours per night.

He then revealed that he had stopped taking aripiprazole for 2 weeks because he had no longer felt ill. He was still taking his lorazepam, however.

Mr. F appeared mildly anxious upon presentation and his affect was blunted. On examination, his thought processes were linear; he was once again hearing voices and experiencing delusions of telepathic control.

The patient was placed back on aripiprazole, 20 mg/d. His behavior on the ward improved dramatically, and the frequency and severity of his delusions and auditory hallucinations decreased gradually.

At discharge, Mr. F's insight was good, his delusions had disappeared, and auditory hallucinations were rare. He was instructed to continue the aripiprazole and was prescribed clonazepam, 0.5 mg bid, for his anxiety and trazodone, 50 mg at bedtime, to help his sleep.

Since then, Mr. F has lived on his own, is working steadily, and has not required hospitalization. He

Related resources

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DRUG BRAND NAMES

Amitriptyline • Elavil
Aripiprazole • Abilify
Benztropine • Cogentin
Chlorpromazine • Thorazine
Clonazepam • Klonopin
Diazepam • Valium
Fluphenazine • Prolixin
Haloperidol • Haldol
Lorazepam • Ativan
Loxapine • Loxitane
Oxazepam • Serax
Thiothixene • Navane
Trazodone • Desyrel

DISCLOSURE

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stopped taking trazodone soon after discharge, but continues taking aripiprazole and clonazepam as prescribed. His hygiene is good, and he is making amends with family members. He attends church every Sunday—free of the messianic delusions that once tormented him. He also stopped abusing alcohol on his own in 1995 and has remained abstinent since.

How can we ensure that patients with schizophrenia keep taking their medications—regardless of whether symptoms are present?

Dr. Canive's observations

Clinical trials measure a drug's efficacy under highly controlled circumstances. In the "real world," however, noncompliance due to intolerability can undermine a medication's effectiveness.

Too often noncompliance—stemming from abatement of symptoms or the emergence of side effects—derails treatment of schizophrenia. Misdrahi et al found that medication noncompliance accounts for 40% of schizophrenia relapses occurring more than 1 year after patients' first hospitalization.[4]

Given aripiprazole's 75-hour half-life, one might not expect to see symptoms emerge so soon after discontinuation. It is possible that:

- Mr. F. abstained from aripiprazole longer than he realized—or admitted
- Unidentified stressful life events also exacerbated symptoms and precipitated hospitalization.

When Mr. F consistently followed his regimen, his positive symptoms abated and he could attempt to live a normal life.

Our patients must understand that schizophrenia is a lifelong illness and that continued adherence to medication—even when symptoms do not exist—is crucial. A strong therapeutic alliance,[5] increased social support, adjunctive cognitive-behavioral therapy, psychosocial interventions,[6] and medications with fewer and less-severe side effects may help patients embrace this message.

References

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