Clinical Case Conference

A Dilemma Born of Progress: Switching From Clozapine to a Newer Antipsychotic

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For patients whose clinical status and quality of life have improved significantly after switching from typical antipsychotics to clozapine, the burgeoning availability of newer antipsychotics poses a paradox. How are we to evaluate the risks and benefits of switching to a newer antipsychotic? Most of the newer antipsychotics have fewer side effects and (putatively) similar efficacy. However, they lack clozapine's extensive track record, particularly its record of efficacy for both negative symptoms and treatment-resistant positive symptoms. This case study suggests some of the issues to be considered when facing this increasingly commonplace clinical dilemma. We present a case of a man with schizophrenia. He appeared much improved 1.5 years after switching from perphenazine to clozapine, but he requested a change to olanzapine because of his long-standing and deeply held objections to weekly blood testing.

CASE PRESENTATION

Mr. A was a 40-year-old single man of mixed African, European, and Cherokee Indian descent who had carried a diagnosis of schizophrenia for 20 years. He was seen biweekly for pharmacological monitoring, supportive psychotherapy, and case management services. He also attended a psychosocial clubhouse program and lived independently in an apartment, where he was visited by a community support worker.

Before Clozapine

Mr. A was born without perinatal complications after a normal full-term pregnancy. His mother was a full-time homemaker, and his father a postal worker. He and his four siblings were raised with both parents present. His mother reported that he met all developmental milestones in a normal time frame and described him as a happy but quiet child who made friends easily in primary school. As an adolescent, he was "quiet and studious." In high school, he was an honors student, developed friendships, and was actively involved in soccer and weight lifting. There was no history of child abuse, and he never used alcohol or drugs.

Mr. A's father suffered from "depression" many years ago, for which he took an unknown medication. A striking feature of that depression is that his father began to "whisper to himself," much as Mr. A did in the early days of his own illness. Mr. A's oldest brother underwent counseling for "nervousness" many years ago, but he was not treated with medication. His mother thinks there were alcoholics among his father's distant relatives, but she is unsure of specifics. She is not aware of any psychiatric problems among other siblings, grandparents, aunts, or uncles. No other family members have been psychiatrically hospitalized, and there is no known family history of suicidal behavior.

Mr. A suffered from asthma as a child, but he was never hospitalized for it and outgrew it before adulthood. He never suffered a seizure, loss of consciousness, or a neurologically significant head injury. He has no history of cardiac or cerebrovascular disease, hypertension, or renal, hepatic, or endocrine disorder. Results of a complete general physical and neurological examination were normal, as were results of serum chemistry, hematology, and thyroid studies. He never had a neuroimaging study.

Mr. A did not report a history of sustained depressed mood or hopelessness. There was no history of a diminished need for sleep with increased energy and no history of grandiosity, elation, sustained irritability, pressure of speech, or flight of ideas. He was never treated with antidepressant or mood stabilizing medication, and there was no history of suicidal, self-injurious, or assaultive behavior.

Mr. A was the only member of his family to attend college. He enrolled as an engineering technology major while still living at home with his parents. During his third semester, at age 18, his parents noticed that he began whispering to himself. He removed the mirror and television from his room without explanation and began to closely inspect the furniture on a regular basis, as if looking for something. One night, he left the house through a window and traveled to a fundamentalist church in another city. Upon his return, he refused his parents' urging to seek treatment. He remained in school for 2 more years, until he was placed on academic leave after failing a course.

At age 21, Mr. A experienced his first psychiatric admission. Just before that admission, his mother reported that he raised all the shades in the house to let in light and drive out evil spirits, who he feared might be listening to his thoughts. All phases of his sleep were disturbed, resulting in severe fatigue. He did not report any psychiatric symptoms throughout his first

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admission, but his records describe bizarre facial grimacing, putting his fingers in his ears when the intercom came on, markedly impaired attention, marked social avoidance, loosening of associations, derailment of thought, and blunted affect. Staff assessed him to be neither manic nor depressed. He refused to take medication. The staff obtained a court order allowing them to treat him with oral trifluoperazine, 30 mg/day at bedtime, as well as benztropine for stiffness and tremor. He was discharged 2 months later with a diagnosis of an "acute schizophrenic episode," and staff described some improvement in his bizarre behavior and formal thought disorder.

Mr. A continued living with his parents for 15 years after his first psychiatric admission, during which time they urged him to be more active and give more attention to his personal hygiene. He was quietly, but continuously, in conflict with his parents. He remained moderately disorganized and socially withdrawn, while continuing to deny that he had an illness. Because of his parents' careful monitoring, he generally took his antipsychotic medication and was able to attend college courses part time. He eventually completed an associate's degree and occasionally worked through temporary agencies at manufacturing jobs. His last employment, at age 33, lasted 2 months.

Mr. A's second and third psychiatric admissions, both precipitated by medication noncompliance, occurred at ages 30 and 33, while he was still living with his parents. The record of his admission at age 30 noted "inappropriate affect, thought blocking, and extreme guardedness about revealing his thought content." He denied that he had an illness but acknowledged that when he stopped taking medication, his concentration became poor. He was discharged with a diagnosis of "chronic paranoid schizophrenia" on a regimen of oral fluphenazine, 5 mg b.i.d., and oral benztropine, 2 mg b.i.d. He remained only intermittently compliant about taking his medication.

At age 37, Mr. A began living outside his parents' home for the first time. He moved into a subsidized apartment of his own and stopped taking his oral fluphenazine almost immediately. The Boston Housing Authority reported that his housekeeping deteriorated markedly. There was so much trash in one room that an inspector was unable to enter it. When he was told that his housekeeping was causing a roach problem, he responded by putting plastic and aluminum foil on the walls, attempting to keep roaches out rather than removing the trash. He put himself at risk of injury by wandering the streets at all hours, and he took in homeless people whom he did not know, in violation of his lease. His mother became alarmed by what records describe as his poor hygiene, poor nutrition, disorganized thoughts, and paranoid delusions.

At age 39, Mr. A was admitted to a psychiatric unit. Records state that he appeared to be responding to auditory hallucinations. He exhibited markedly disorganized thought, poverty of speech, blunted affect, and social withdrawal. The institution petitioned for full guardianship, and at his request, a court-appointed attorney, rather than a family member, became his guardian. He was then treated with a regimen of oral perphenazine, 24 mg/day in the morning and 32 mg/day at bedtime, and oral benztropine, 1 mg b.i.d., for extrapyramidal symptoms.

He was subsequently transferred to a day hospital program and psychiatric shelter, both located at the Massachusetts Mental Health Center. One week after admission, Mr. A left against medical advice, reoccupied his apartment, and stopped taking his medication. When he was involuntarily hospitalized 10 days later, he stated that he needed medication for his "jumbled thoughts." This is the first documented instance of Mr. A requesting medication to help his thinking. During this admission, he learned that he had been evicted from his apartment.

He returned to the day hospital and shelter program at the Massachusetts Mental Health Center, where he remained unwaveringly preoccupied with regaining his own apartment, speaking frequently of the preeminent importance of "my independence." Initially, he was treated with perphenazine, which he complained caused "excretions" that he could not further define. (On good days, he would say, "The excretions are slow.") He required benztropine treatment for parkinsonian symptoms.

Mr. A rarely spoke spontaneously, and his statements were usually brief, vague, idiosyncratic, and disorganized. When asked how he had spent his time after a weekend, he typically would say, "I rested around," and was unable to elaborate. He had scant insight into his illness, explaining his long unemployment with vague statements such as, "I just was not in a position for it." He remained paranoid, saying that he could not live in a group home because "I can't trust anybody there." He was inattentive in team meetings, was interpersonally disengaged throughout the day, sought out little activity, and expressed no interests or desires (apart from wanting his own apartment).

The typical neuroleptics with which Mr. A had been treated included haloperidol, trifluoperazine, thioridazine, and fluphenazine—all of which had produced significant stiffness and tremor, requiring up to 4 mg/day of benztropine. Given the substantially disabling impact of his symptoms, we proposed a trial of clozapine. Mr. A was initially adamantly opposed to trying clozapine. His opposition was due less to any of its known side effects than to his delusional conviction that blood testing, even using alternate arms on alternate weeks, would "destroy my veins." However, with his reluctant agreement and the consent of his guardian, a trial of clozapine was initiated. After a 3-month cross-taper, which began in June 1995, during which clozapine treatment was started and perphenazine discontinued, his clozapine blood level, with an oral dose of 500 mg/day at bedtime, was 260 mg/dl.

Taking Clozapine

The first changes noted after Mr. A started taking clozapine were more sleepiness and salivation. However, after 6 to 8 weeks, his affect began to brighten, and he gradually became less withdrawn. After about 4 months, he acknowledged that his thoughts were clearer. His thoughts seemed better organized, and for the first time, he began to participate spontaneously in day hospital team meetings. His participation demonstrated much better attention to what was being discussed, and staff were astounded by his efforts to offer support and understanding to other patients. He began to attend a psychosocial clubhouse where, with encouragement, he participated in cooking, cleaning up, and other community projects.

For the first time, he began to acknowledge that he had a mental illness and to call it "schizophrenia." He began to express hope of one day returning to work and finding a girlfriend. While acknowledging that his thinking was clearer with clozapine, he consistently maintained that perphenazine was the medicine that had helped him the most. He continued to fear the ef-

fects of weekly blood tests and to believe that clozapine was "one of those medicines that just destroys your health." He still maintains these beliefs. These limitations of insight have served to spare Mr. A the emotional distress that often accompanies "awakening" because of clozapine, notwithstanding the significant improvements in his functioning and quality of life (1).

He remained in a psychiatric shelter for 16 months, refusing offers of a supervised group home. Finally, in July 1996, he moved into his own apartment, which he has successfully maintained. He reported that he faithfully continued to take his oral clozapine, 500 mg/day at bedtime, as prescribed. This report is consistent with our observation of no decline in his clinical status and a clozapine blood level of 332 mg/dl 2 months after he moved into his apartment. He consistently refused offers of adjunctive medications to help with his daytime sedation and excess salivation, stating politely, "No, no. I don't want any more drugs."

In our efforts to persuade Mr. A to start and remain on a regimen of clozapine, we repeatedly stressed our view that it was the best drug available for him. We assured him that we could discuss switching to another medication if something potentially better came along. This approach had the unintended effect of helping to foster his preoccupation with "those new drugs coming along."

Nonetheless, we shared his conviction that he was entitled to as much choice in his treatment as reasonable clinical judgment would permit. While we clearly did not share his fears about weekly blood testing, we thought he was entitled to be free of them if a reasonable alternative existed. We also remained concerned about the significant negative impact of his continued and obvious daytime sedation. Given his robust clinical response to clozapine, we would not have proposed a change to olanzapine simply to avoid the risks of agranulocytosis and seizures. (Both were minimal after 1.5 years of taking a stable dose of 500 mg/day of clozapine.)

When olanzapine was released for general use in October 1996, we discussed the risks of changing medication in detail with Mr. A and his guardian. We emphasized the possibility of relapse and rehospitalization, the possible need to resume clozapine treatment, and the possibility that clozapine would not work as well the second time. He might never be as well again. Both he and his guardian wished to proceed. To reduce the risk of destabilizing him, we planned a very gradual cross-taper. We also increased the frequency of his outpatient appointments from every other week to weekly. In January 1997, 1 week after adding oral olanzapine, 5 mg/day at bedtime, to his long-standing dose of oral clozapine, 500 mg/day at bedtime, we began reducing his daily clozapine dose by 50 mg each week. His dose of oral olanzapine was increased to 10 mg/day at bedtime when his dose of oral clozapine was reduced to 400 mg/day at bedtime, and his dose of oral olanzapine was again increased, to 15 mg/day at bedtime, when his dose of oral clozapine was reduced to 300 mg/day at bedtime. After Mr. A reached a clozapine dose of 100 mg/day, we decreased the rate of reduction of his daily dose to 25 mg each week. Three full months after starting this cross-taper, Mr. A took his last 25-mg dose of clozapine, and he has been receiving oral olanzapine, 15 mg/day at bedtime, and no other medications since April 1997.

Switching to Olanzapine

We have observed no increase in any positive or negative symptoms of schizophrenia since Mr. A switched to a regimen of olanzapine. The core of his recent psychopathology has been moderate disorganization of thought, manifested by conceptual vagueness, an idiosyncratic use of language inconsistent with his educational background, and occasional derailment. His enduring beliefs that weekly blood tests were not merely uncomfortable or inconvenient but damaging and that clozapine was detrimental to his health demonstrate some persisting, though well circumscribed, difficulty with reality testing. He is not otherwise frankly paranoid but remains guarded about new experiences and suggestions. We have seen no evidence of hallucinations or ideas of reference, and he continues to recognize that he has had a long history of problems. He persists in his negative attitude toward antipsychotic medications, despite recognizing the benefits he has derived from them. This demonstrates limitations in his insight and judgment. He often will grasp at very concrete ideas that he cannot explain, such as believing that a certain number of pills is right for him, regardless of his clinical response. To alleviate his residual symptoms, we recommended an increase from 15 to 20 mg of olanzapine daily. He has thus far declined this advice, explaining only that 20 mg would be "too much" for him.

Nonetheless, some significant improvements in his functional status have been evident since he switched to olanzapine. He is clearly less sedated, and for this reason, his attention and susceptibility to derailment appear improved. Staff at his psychosocial clubhouse report that he now attends more frequently (about three times weekly) and that he now takes the initiative in a wider range of community activities (including cooking, cleaning, and going to the local video store to select movies for the group). As a result of these changes, he has become one of the most central members of that community. Meanwhile, he reports that he is sleeping 8 to 9 hours nightly (versus 11 to 12 while taking clozapine) and that he feels well rested during the day. He has been attending church and visiting his family more frequently, and he has begun to talk about concrete strategies for finding a part-time job.

DISCUSSION

Mr. A's functional improvement with clozapine was dramatic. He presented initially with bizarre and paranoid delusions (e.g., fearing that evil spirits were listening to his thoughts), as well as with evidence of auditory hallucinations and marked thought disorganization. Typical neuroleptics helped to reduce his delusions and hallucinations but were less useful in improving his thought disorganization. A regimen of clozapine later led to substantial improvement in his negative symptoms and further improvement in his cognitive status. This formerly profoundly withdrawn, seriously disorganized, and pervasively anhedonic man became a warm and engaging, if still mildly disorganized, member of his community. He went from living in a psychiatric shelter to achieving his cherished goal of living independently in his own apartment for the first time. Once isolated and socially indifferent, he became an active member of a psychosocial clubhouse. Aspirations to return to work and find a mate have emerged, both of which are plausible for the first time in years, even if not yet fully within his grasp.

Without benefit of the knowledge we have now of Mr. A's robust response to olanzapine, was it reasonable to put many of his hard-won gains at risk by agreeing to honor his re-

quest to switch from clozapine to olanzapine? The case against doing so was strong. His primary reason for wishing to stop taking clozapine was his conviction that blood tests were causing cumulative insidious harm to his health. Such a false belief clearly does not justify such a major treatment decision. Furthermore, assenting to a request that is informed by distorted reality testing carries the risk of being understood by a patient as an endorsement of his or her reasoning, regardless of what we may tell a patient to the contrary.

A second argument in favor of staying with clozapine specifically is the evidence supporting its efficacy for both negative symptoms and treatment-resistant positive symptoms. This record is obviously far more extensive than that available for any of the newer antipsychotics (2–5). One or more of these newer agents may turn out to be "clozapine without agranulocytosis," but this is at best wishful thinking at this point. Our collective anecdotal experiences at the Massachusetts Mental Health Center with changing previously treatment-resistant patients (who improved with clozapine treatment) to newer antipsychotics has been decidedly mixed. A significant portion of these patients have not done as well, and some have failed to respond as robustly when they started another regimen of clozapine.

A final argument for not risking a medication change was Mr. A's history of limited insight. He did not recognize the improvement apparent to everyone else after he switched from perphenazine to clozapine. If he had not appeared to us to do as well on olanzapine as clozapine, would he have recognized this? How difficult would it have been to persuade him to resume taking clozapine? Guardianship or not, compliance with taking oral medication is ultimately (and literally) in the patient's hands.

Notwithstanding these arguments for resisting Mr. A's wish to change his medication, we felt that the reasons for cooperating with him were more compelling. Physician-patient collaboration is the foundation of long-term treatment adherence (6–8). Both our alliance with Mr. A and his long-term adherence with taking antipsychotic medication were likely to be enhanced if he were a respected partner with the power to influence his treatment plan.

Psychologically, at the age of 40, Mr. A was enthusiastically engaged in tasks of independence more typical of late adolescence and early adulthood, a venture derailed 20 years earlier by the effects of his illness. The intensity of his insistence on acquiring an apartment of his own reflected the intensity of his long struggle to assert his autonomy in relation to his parents. His success in achieving this goal provided an enduring boost to his self-esteem and stimulated his initiative in maintaining regular contact with others. Our support in helping him attain this goal immeasurably strengthened our alliance with him. We believed that we should make every reasonable effort to support his self-determination.

Clearly, for a psychotic patient under guardianship, the value of self-determination must be understood in the context of reasonable clinical judgment regarding his or her best interests. In our view, the use of olanzapine for a patient such as Mr. A was reasonable. In terms of basic pharmacology, its receptor affinity profile closely resembles that of clozapine, with the added advantage of being less antihistaminic. These attributes suggested a reasonable hope for similar therapeutic efficacy with less sedative effect (9–11). Furthermore, olanzapine has been shown to have efficacy comparable to that of haloperidol for positive symptoms and superior to that of haloperidol for negative symptoms, without extrapyramidal symptoms (12). Thus, our concern about possible relapse into florid positive symptoms was relatively low, and our hope to maintain the improvement in his negative symptoms seemed well grounded.

We also felt that it was important to keep in mind the principle of idiosyncratic pharmacological response. In psychiatry, especially, we observe a wide range of patient responses to agents of well-validated efficacy for their diagnoses. Even if subsequent studies were to demonstrate that a significant percentage of patients who switched from clozapine to newer atypical antipsychotics do not do as well, there will certainly be exceptions. Among the factors known to mediate a patient's response to treatment is the patient's attitude toward the treatment. Regardless of "objective" efficacy, subjective response to antipsychotic medication has been found to be an independent predictor of long-term outcome in schizophrenia, an effect only partially accounted for by treatment adherence (13). Mr. A's positive attitude toward olanzapine (and negative feelings about clozapine) probably made a positive outcome with olanzapine (and eventually a negative outcome with clozapine) more likely (14).

What if we had been wrong? Let us assume first that olanzapine had turned out to be slightly less effective for his symptoms than clozapine. We would still need to weigh the relative importance of a slight increase in his symptoms against the benefits of our collaboration with his request for our treatment alliance and his long-term compliance. But what if we had been very wrong and he had been dramatically worse while taking olanzapine? We hope he would have agreed to resume taking clozapine (a contingency to which he had agreed in advance), and we hope it would have worked as well for him the second time. However, we had no guarantees on either account.

This case raises intriguing diagnostic questions as well as dilemmas of treatment born of recent progress in psychopharmacology. First, a number of features seem atypical for a patient with a 20-year history of schizophrenia: his warmth, his engaging manner, and the relative preservation of his social graces. Patients suffering from schizophrenia for so long typically show much more deterioration of interpersonal skills (15). This sort of presentation is likely to become more common with the increasing use of atypical neuroleptics and their frequently salutary effect on negative symptoms (2, 16, 17). Given 20 years of occupational and social impairment and the absence of a history of a major affective episode or a general medical or substance-related cause for his difficulties, schizophrenia is the most reasonable diagnosis for Mr. A.

The second diagnostic issue raised is what sort of schizophrenia does Mr. A have? This question is of more than academic interest, since we know that the subtype at the index episode of schizophrenia has prognostic significance and, thus, implications for treatment (18). Medicated as Mr. A now is, the DSM-IV subtype that seems to describe him best now is disorganized. However, given the prominence of hallucinations and frank delusions he suffered when he was unmedicated, one has to ask if this subtype was undifferentiated or even paranoid in the past. If so, should we think of his current subtype as a residual form of undifferentiated or paranoid schizophrenia? Or is it more reasonable to suggest that his subtype has changed, at least in part because of his medication?

CONCLUSIONS

While second-generation atypical antipsychotics promise to improve the symptoms, quality of life, and treatment adherence of many patients with chronic psychotic disorders, for patients already significantly improved after switching from a typical neuroleptic to clozapine, a number of issues must be considered before they switch to a newer antipsychotic. These issues include a given patient's preference, competence, diagnosis, and history of symptoms and pharmacological response. Equally important is the evidence of efficacy for positive and negative symptoms and side effect profiles of the agents under consideration. Treatment adherence and the therapeutic alliance are also important considerations. A thoughtful review of risks and benefits will no doubt favor continuing a regimen of clozapine in some cases and trying a newer antipsychotic in others.

REFERENCES

1. Duckworth K, Nair V, Patel JK, Goldfinger SM: Lost time, found hope and sorrow: the search for self, connection and purpose during "awakenings" on the new antipsychotics. Harv Rev Psychiatry 1997; 5:227–233
2. Kane JM, Tamminga CA, Schooler NR, Casey DE: Choosing among old and new antipsychotics. J Clin Psychiatry 1996; 57: 427–438
3. Kane J, Honigfeld G, Singer J, Meltzer H: Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988; 45:789–796
4. Breier A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerfelt A, Carpenter WT Jr: Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. Am J Psychiatry 1994; 151: 20–26
5. Marder SR: Management of treatment-resistant patients with schizophrenia. J Clin Psychiatry 1996; 57(suppl 11):26–30
6. Falloon IRH: Developing and maintaining adherence to long-term drug-taking regimens. Schizophr Bull 1984; 10:412–417
7. Eisenthal S, Emery R, Lazare A, Udin H: "Adherence" and the negotiated approach to patienthood. Arch Gen Psychiatry 1979; 36:393–398
8. Corrigan PW, Liberman RP, Engel JD: From noncompliance to collaboration in the treatment of schizophrenia. Hosp Community Psychiatry 1990; 41:1203–1211
9. Beasley CM, Sanger T, Satterlee W, Tollefson G, Tran P, Hamilton S, Olanzapine HGAD Study Group: Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology (Berl) 1996; 124:159–167
10. Meltzer HY, Fibiger HC: A new atypical antipsychotic drug. Neuropsychopharmacology 1996; 14:83–85
11. Casey DE: Side effect profiles of new antipsychotic agents. J Clin Psychiatry 1996; 57(suppl 11):40–45
12. Beasley CM, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S, Olanzapine HGAD Study Group: Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996; 14:111–123
13. Awad AG, Hogan TP: Subjective response to neuroleptics and the quality of life: implications for treatment outcome. Acta Psychiatr Scand Suppl 1994; 380:27–32
14. Budd RJ, Hughes ICT, Smith JA: Health beliefs and compliance with antipsychotic medication. Br J Clin Psychol 1996; 35: 393–397
15. Sobel W, Wolski R, Cancro R, Makari GJ: Interpersonal relatedness and paranoid schizophrenia. Am J Psychiatry 1996; 153: 1084–1087
16. Weldon P, Aquila R, Standard R: Atypical antipsychotic drugs and long-term outcome in schizophrenia. J Clin Psychiatry 1996; 57(suppl 11):77–82
17. Colonna L: Antideficit properties of neuroleptics. Acta Psychiatr Scand Suppl 1994; 380:77–82
18. Kendler KS, Gruenberg AM, Tsuang MT: Outcome of schizophrenic subtypes defined by four diagnostic systems. Arch Gen Psychiatry 1984; 141:149–154