Chronic Schizophrenia: Response to Clozapine, Risperidone, and Paroxetine

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Dr. Patel: We describe here a woman with a diagnosis of chronic schizophrenia. Her case history, which spans a period of more than 30 years, demonstrates a "neurodevelopmental" pattern of the unfolding of negative and positive symptoms. It also illustrates an unusual treatment response to the combination of clozapine, risperidone, and paroxetine.

CASE PRESENTATION (Dr. Patel)

Ms. A is a 46-year-old single woman who resides in a supervised community residence and participates in a day hospital program at the Massachusetts Mental Health Center. Her current medication regimen includes 275 mg/day of clozapine; 6 mg/day of risperidone; and 50 mg/day of paroxetine.

Psychiatric History

The patient was born in China of Chinese parents after a full-term normal delivery; there were no perinatal complications. The mother had been treated with penicillin for a sore throat during the first trimester. Soon after the patient's birth, the family left China and lived in several Asian countries over the next 10 years. As an infant, Ms. A cried frequently and would at times turn blue while crying; this behavior continued until she was about 15 months old. From a young age, she was a stubborn child, but she was very meticulous and unusually clean.

The family emigrated to Florida when the patient was 10 years old. In Florida, she apparently was an A student but was noted to be shy and to lack initiative. The family moved to Massachusetts when the patient was 12 years old. At this point the patient's school performance began to decline and she had an insidious onset of psychiatric problems. The initial symptoms included moodiness, social isolation, and "spaciness." She was not able to concentrate, spent hours doing very little, and was underachieving at school. According to her parents, she had problems with comprehension and composition. She became progressively more hostile at home and had frequent temper tantrums and conflicts with her mother.

By age 15, the patient was showing increasingly bizarre behavior. She would spend long periods combing her hair and talking to herself in the mirror. She was socially isolated and withdrawn. At times, she could not follow directions in school and appeared confused; teachers had difficulty communicating with her. She had a brief psychiatric hospitalization when she seemed to be hallucinating. She was given a diagnosis of "adolescent turmoil reaction" during this hospitalization.

When she was 16 years old, the patient's hallucinations and social withdrawal increased, and she was treated with chlorpromazine as an outpatient. At age 17, she refused to take her medication and, following an argument with her mother, was readmitted to the hospital in a mute and catatonic state. Following treatment with low doses of chlorpromazine (100 mg/day), she began to speak and exhibit echolalia, thought blocking, and circumstantiality; she described derogatory voices that commanded her to kill herself. Neurological examination (including sleep-deprived EEG) was unrevealing. The neuroleptic dose was increased to a combination of 400 mg/day of chlorpromazine and 20 mg/day of trifluoperazine. Although there was some gradual improvement, after a 6-week hospitalization she still needed further inpatient treatment and was transferred to a state hospital.

Ms. A remained at a state hospital from age 18 to age 26. During the initial years there, she was continuously psychotic and had frequent conflicts and fights with other patients. She seemed childlike, with screaming spells, angry outbursts, and temper tantrums. She lacked initiative and was difficult to communicate with; she seemed to be hallucinating and was oblivious to her surroundings. Between the ages of 20 and 23, she was given trials of perphenazine, thiothixene, prochlorperazine, and haloperidol without substantial benefit. Use of a behavioral treatment plan was not helpful.

At age 23, following the administration of 500 mg/day of mesoridazine, Ms. A seemed to improve somewhat. The intensity of her auditory hallucinations and delusions decreased, although they never disappeared totally, and she was less irritable and more redirectable. By age 24, she was working at a hospital job and was given passes to visit her parents on weekends. Over the next year, her work functioning continued to improve. However, her hygiene remained very poor, she needed assistance with activities of daily living, and she continued to be socially isolated. In addition, she had frequent episodes of self-induced vomiting, which had developed initially at age 18. By age 26, after a trial of fluphenazine decanoate, she developed a severe tremor and evidence of tardive dyskinesia. Consequently, her medication regimen was switched back to mesoridazine, and, over the next year, her psychosis and social functioning improved to some degree, to the point that she was able to live in a supervised setting in the community.

Although Ms. A lived in a variety of quarter-way and halfway houses over the next 12 years, she continued to have numerous hospital admissions. When hospitalized, she would be psychotic, delusional, and preoccupied with somatic concerns and symptoms. Her thought process was often illogical, tangential, and incoherent, and her behavior was often disruptive. While in the community, she was often assaultive and would steal from other patients. Her ongoing delusion of having an eel in her throat and stomach led to many somatic complaints and multiple attempts at self-induced vomiting. Compulsive behaviors, such as touching things in a repetitive manner, were evident. Medications employed over these years included the neuroleptics mesoridazine, loxapine, and fluphenazine (oral and depot) for the treatment of psychosis; lithium carbonate in an attempt to potentiate the efficacy of the neuroleptics, as well as to provide

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for behavioral control; and the β blocker nadolol for behavioral control.

From the ages of 39 to 43, Ms. A was readmitted for a period of 4 years after assaulting a 3-year-old child without inflicting serious injury. In the hospital, she was irritable, often screamed and yelled, and exhibited random or focused assaultive behavior. Treatment with fluphenazine decanoate and lithium (plus low doses of imipramine for depressive symptoms) was not helpful. Moreover, she had a very severe parkinsonian tremor—she could not drink from a cup without spilling the liquid. At age 41, all psychopharmacological agents were withdrawn in preparation for a trial of clozapine.

With clozapine treatment, there was progressive improvement in her mental status. Her psychosis and assaultive behavior decreased, as did her episodes of vomiting; moreover, her tremor improved dramatically and she had only very mild tardive dyskinesia. She was eventually able to again live in the community in a quarter-way house. Once outside of the hospital setting, however, her compliance with clozapine therapy became erratic. When she missed her medication, she would quickly decompensate, leading to frequent brief admissions with worsening psychosis, thought disorder, and agitation, as well as negativistic and uncooperative behavior. Even while she was taking clozapine and doing better, however, her repetitive checking behaviors worsened.

On one of her readmissions, the clozapine was switched back to fluphenazine because of difficulties controlling clozapine-induced hypotension and tachycardia, as well as her pattern of erratic use of the drug. However, after clozapine was discontinued, the length of her hospital stays began to increase and her overall clinical status worsened.

When Ms. A was 45, clozapine was started again a number of months after it had stopped. Valproic acid was added to the clozapine in the hope that it might augment its effects. However, she continued to have thought blocking and disorganized speech with this combination; she was obsessed with food and occasionally was confused and regressed. At this point, a decision was made to introduce the then-new neuroleptic risperidone and simultaneously taper the valproic acid and clozapine while Ms. A was under inpatient observation at the Research and Evaluation Unit at the Massachusetts Mental Health Center. (It was hoped that risperidone might provide for better symptom control than clozapine and valproic acid, while producing fewer side effects.)

During the simultaneous taper of clozapine and introduction of risperidone, there was a progressive and substantial improvement in Ms. A's capacity to communicate; she also became more organized. Because of this improvement, the taper of clozapine was held at 275 mg/day, and the dose of risperidone was kept at 6 mg/day. After about 12 weeks of this combination, despite apparent improvement, there also seemed to be a gradual worsening of her preexisting compulsive behaviors, such as checking and touching. Because these behaviors were interfering with her daily activities, paroxetine was judiciously added at 10 mg/day and the dose slowly increased, reaching a maximum dose of 50 mg/day after a period of 1 month. While taking paroxetine, the patient experienced a marked decrease in her repetitive and compulsive behavior. After an extensive aftercare plan to ensure that she would comply with the treatment (including incentives for her to participate in her treatment program), she was able to move back to a supervised community residence.

In the 6 months since her discharge, Ms. A has continued to take her medications and has been able to sustain herself in the community (with considerable assistance provided by her family and the residence staff). There has been no assaultive behavior. She has almost entirely stopped smoking. There has been a striking decrease in the level of her overall apathy; her ability to initiate and to participate in structured activities has dramatically improved. Despite a substantial weight gain, both she and her family report that she is doing very well on the combination treatment. The family says that she has not appeared this well since she was a teenager.

Medical History

Ms. A's history is positive for pulmonary and abdominal tuberculosis at age 20; she received a 3.5-year regimen involving four antituberculosis medications. Recent examinations have revealed no recurrence. Her episodes of vomiting (sometimes self-induced) began at age 18 and continued until she started the current medication regimen. Her teeth were extracted in her 20s due to poor dental hygiene. Tardive dyskinesia was first noted at age 26. During treatment with lithium (in her 30s), she developed nephrogenic diabetes insipidus, and she had four episodes of dehydration with lithium toxicity. Her menstrual periods have been irregular, with times of amenorrhea. During treatment with clozapine alone, her periods normalized. On the current regimen of clozapine, risperidone, and paroxetine, she has once again developed amenorrhea. One year ago, at age 45, she was noted to have a nonmalignant cold thyroid nodule, which is being closely monitored.

Substance Use

The patient, a long-time cigarette smoker, has recently dramatically reduced her tobacco use (on the new psychopharmacological regimen). She is a heavy coffee drinker and freely consumes other caffeinated beverages as well. She denies use of alcohol or illegal substances.

Family History

The maternal grandfather developed a chronic psychosis in his 30s. The mother's cousin had an "inappropriate affect" beginning in his 20s, and her uncle became psychotic while witnessing torture of other relatives in China. The patient's father has been noted to be anxious with obsessive and compulsive traits.

Laboratory Investigation

At present, results of routine blood work are unremarkable. A head computerized tomography (CT) scan and an EEG were done when the patient was 46 years old. The CT scan showed minimal enlargement of the third, lateral, and fourth ventricles, plus moderate cerebral atrophy involving the frontal lobes and the insular cisterns bilaterally; the EEG was read as normal. Results of recent neuropsychological testing were consistent with frontal lobe dysfunction: the patient was stimulus bound, lacked an abstract attitude, and had little capacity to monitor herself. Despite attentional/executive system dysfunction, she passively attended to new information and could make sense of minor aspects of a situation. Verbal and visual memory deficits were consistent with severe, chronic schizophrenia. A comparison of the WAIS-R full-scale IQ and standard scores on the Wide-Range Achievement Test—III reading subtest suggested at least a 20% loss of intellectual functioning, most likely secondary to her schizophrenic disorder.

PATIENT INTERVIEW (Dr. Salzman)

The patient entered the conference room smiling broadly and waving at a number of people in the room. She was a well-groomed and appropriately dressed woman who appeared somewhat older than her stated age, in part because she was edentulous. She made good eye contact and seemed relaxed, although her interaction with the interviewer seemed somewhat mechanical. She spoke in a monotone, and only in response to direct questions. Her answers to questions were brief and at times vague; she was unable to provide a clear longitudinal history. Her affect seemed constricted; she said her mood was good. She denied hearing voices, although she said that she had heard them in the past. She denied thought broadcasting, thought insertion, or delusions of control or influence, but she smiled when asked if she had experienced these things in the past. When asked whether she had an eel in her throat, she said she was "no longer ill." When asked what she liked to do, she said she was a good cook. As she spoke more about food, her thought process became tangential and circumstantial. She was oriented in three spheres. Her interpretation of proverbs was concrete. The patient denied any unusual movements or side effects of the medications. She exhibited no tremor or symptoms of tardive dyskinesia.

DISCUSSION (Dr. Tsuang)

This is an excellent teaching case. Without much question, Ms. A meets the

DSM-IV criteria for schizophrenia. Moreover, she also seems to demonstrate the prototypical course of symptom development that has led many investigators to believe that schizophrenia is a neurodevelopmental disorder (1, 2).

Although there is little in her history to suggest perinatal problems or serious difficulties in her early years, we learned that her mother had been treated with penicillin for a sore throat during the first trimester and that up to the age of 15 months the patient would at times turn blue from crying. Could either of these factors have been related to her later problems? Clearly, there is no way to know the answer. The patient comes from a family with some apparent history of psychosis, and, consequently, she could carry a genetic predisposition for schizophrenia.

Although she was an excellent student as a young girl, she began to demonstrate an insidious development of a psychotic process during her teenage years. Initially, her most prominent symptoms were negative ones—lack of initiative, social withdrawal, and isolation. Positive symptoms of psychosis developed later. Weinberger (1, 3) has proposed that mesocortical dopaminergic system deficits could produce negative symptoms but might lead in adolescence to the eventual explosion of positive symptoms through lack of inhibition of the mesolimbic dopaminergic system. This patient seems to have followed that pattern.

I have asked our guest, Dr. Heinz Hafner, Head of the Schizophrenia Research Unit, Central Institute of Mental Health, Mannheim, Germany, to comment on the initial development of psychotic symptoms in this woman.

Dr. Hafner: The patient described by Dr. Patel and interviewed by Dr. Salzman had been noted to develop an insidious onset of psychiatric problems beginning around age 12. Her symptoms at that time were moodiness, social isolation, underachieving in school, and problems with comprehension and hostility. All these symptoms, except hostility, are among the 10 most frequent signs of schizophrenia (as noted by patients themselves) (4). I agree entirely with Dr. Tsuang that she meets the classic (DSM-IV) criteria for schizophrenia.

However, in at least one way, her case is not classic. Her age at onset, her course, and, indeed, her chronicity are more characteristically seen in men than in women. Her symptoms began at age 12, considerably earlier than the average age at onset for women, which peaks in the late 20s (with a second smaller peak in the mid-40s). By contrast, the age at onset for men peaks in the early 20s, about 4 years before the first peak in women (5). A number of investigators have suggested that the later age at onset in women may be due to a "protective effect" of estrogen; in that regard, the second peak in the 40s may relate to lower estrogen levels that occur with the onset of menopause. Seeman and Lang (6) have noted that women also seem to have a better response to neuroleptics than men. In that way as well, this patient is somewhat unusual.

Dr. Salzman: Regarding the issue of Ms. A's presentation being more characteristic of men than women, Berman et al. (7, 8), from Dr. Green's group, have noted that patients with obsessions and psychosis have a more severe schizophrenic syndrome than those without such symptoms. Perhaps the presence of her clear obsessional symptoms puts her more into the "male" severity category.

Dr. Tsuang: Thank you both for your comments. I believe it is important to recognize that although her positive symptoms, such as hallucinations and delusions, have generally caused her to be hospitalized, control of many of these symptoms with the current regimen has not corrected the negative (or deficit) syndrome but may well have lessened its severity. Our group has speculated that the negative syndrome is primary and may be the inherited characteristic of the disorder (2). Following along Weinberger's model, it is possible that we could prevent the eventual development of psychosis in at-risk people if we could figure out a way to correct the prefrontal cortical deficit. Perhaps the new generation of antipsychotic drugs may be worth testing in this regard.

I would now like to ask Dr. Green to comment on the remarkable response of this patient's psychotic and obsessional symptoms to the current unusual psychopharmacological regimen.

Dr. Green: This patient's history of neuroleptic treatment reads like the prototypical "treatment resistant" case, but there are a few interesting and unusual aspects to it.

First, she had symptoms of psychosis as well as obsessions and compulsions from an early age. Dr. Ileana Berman from our group has reported data suggesting that patients with combined psychotic and obsessional features are among the most treatment refractory (7, 8). Moreover, we have demonstrated in a pilot study that patients with such symptoms may improve when the "antiobsessional" drug clomipramine is added to an existing regimen of a typical neuroleptic (7). As Dr. Salzman noted, perhaps the severity of her syndrome (somewhat unusual in a woman) may be partly due to her obsessional and compulsive traits.

Second, she responded to the unusual combination of clozapine, risperidone, and paroxetine. With clozapine alone, she seemed to do better than when she was treated with typical neuroleptics. However, there was an increase in her "food obsessions" with clozapine treatment. Given clozapine's serotonin receptor antagonistic effects, it should perhaps not be unexpected that it could increase obsessional or compulsive symptoms, as has been suggested by anecdotal reports of a number of investigators (9–11). In this patient the combination of clozapine and risperidone was arrived at serendipitously during the transition between the two drugs. Whether the decrease in her confusion and increase in her ability to communicate was a result of the lowering of the clozapine dose or the activating effect of risperidone is not clear. There is also no way to know whether she would have responded to risperidone alone if the clozapine had been completely tapered. What we do know is that the combination seemed to lead to an increase in the checking and touching rituals. (Interestingly, there have been two reports suggesting that risperidone, like clozapine, may increase obsessional symptoms in psychotic patients [12, 13]). Judicious addition of the specific serotonin reuptake inhibitor (SSRI) paroxetine definitely lessened the obsessive and compulsive symptoms and resulted in a dramatic overall improvement. Despite the apparent benefit from the combination in this case, however, clinicians must remember that paroxetine (and certain other SSRIs) can increase clozapine blood levels and thereby cause an increase in its side effects. (In this patient, the clozapine dose was relatively low before the paroxetine was added; however, the combination should be used with some caution [14].) Nonetheless, I find it intriguing to wonder how many patients who appear to be clozapine (or risperidone) nonresponders are actually experiencing an increase in obsessional symptoms (even with a lessening of psychosis itself) during clozapine or risperidone treatment. This is a study waiting to be done.

Third, I would like to comment briefly on the effects of neuroleptics on

the menstrual cycle. Neuroleptic use is associated with hyperprolactinemia and menstrual abnormalities in women (15, 16). Moreover, estrogen levels in neuroleptic-treated women are often low—perhaps secondary to the hyperprolactinemia caused by these drugs (17, 18). This patient was amenorrheic while taking typical neuroleptics, but while taking clozapine, which does not elevate prolactin substantially (19), her menstrual periods were regular. Interestingly, when another strong dopamine 2 antagonist (risperidone) was added to the regimen, once again she developed amenorrhea. The comparative effects of clozapine and other neuroleptics (including risperidone) on ovarian function is an area that deserves further study.

Until recently, the fact that typical neuroleptics elevate prolactin levels has mainly been a subject of research interest; for example, prolactin levels have been measured as an indication of "neuroleptic bioavailability" (18). Although hyperprolactinemia can have clinical consequences, the clinical effects have not been carefully studied because all typical neuroleptics elevate prolactin. However, with the new generation of antipsychotic drugs on the way (some of which, like clozapine, do not elevate prolactin), we may be in a position to assess whether the prolactin elevation routinely produced by typical neuroleptics has some bearing on the response to these drugs—either their therapeutic potential or their side effects.

Finally, it is noteworthy that the patient has dramatically decreased her smoking and no longer seems to have symptoms of a movement disorder. McEvoy et al. (20) recently reported that clozapine may be associated with decreased smoking. If this continues to be reported, it may be a very important effect of clozapine in patients with schizophrenia. Obviously, the movement disorder effect is also quite important clinically. As has been reported by a number of groups, giving clozapine results in a decrease in extrapyramidal symptoms and allows tardive dyskinesia to settle down (21); moreover, risperidone (at a dose of 6 mg/day) is associated with a low rate of extrapyramidal symptoms (22).

Dr. Tsuang: We have focused the discussion of this case on the new scientific aspects of the theory of schizophrenia and the development of a new pharmacology for the syndrome. But it would be wrong to forget the time-honored lessons about working with such patients. As this case nicely demonstrates, patients with severe psychiatric disorders require a multidisciplinary staff that can provide long-term continuity of care. Acute relapses in these patients can often be forestalled in such an integrated treatment program. Optimal treatment can be provided when there is close communication among community programs, outpatient treatment centers, responsible clinicians, and inpatient staff—especially, as seen in this case, when the family is also supportive of the overall program. For the primary therapist, the development of a therapeutic alliance is crucial. How could anyone convince the patient to try new medication regimens without having her trust? In addition, therapeutic patience is essential. Patients who improve with new therapeutic agents must be given time to adjust to their new skills. We have to make sure that our psychosocial treatments are as well thought through as our medication combinations for these patients. A patient recovering from years of psychosis has to reenter the world. Unfortunately, as this patient demonstrates, the diminution of psychosis does not mean the loss of all negative symptoms. Social skills training programs would seem to be essential if patients like this are to achieve the full potential provided them by our new psychopharmacological wonders.

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