Reversal of Schizophrenia Without Neuroleptics

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It commonly is believed that reversal of schizophrenia is accomplished primarily through neuroleptic drug treatment, but this belief can be maintained only by ignoring a great deal of material published in the historical and scientific literature. A brief historical review is provided which reveals that neuroleptics became the treatment of choice after 2 centuries of physically abusive "treatments" that more resembled torture than treatment. The rationale offered for these abuses was that insanity was primarily a physical disorder and that without these methods no recovery was possible. A review of long-term studies of people diagnosed with schizophrenia is provided to show, however, that schizophrenia reverses naturally in most people, with the highest rate of recovery occurring in a nonindustrialized country where no neuroleptics were used. Chlorpromazine was the first neuroleptic introduced, and, after excluding both studies with less than 1 year of follow-up and drug-withdrawal studies, only three studies with a randomized, placebo-controlled design were found. These three studies are reviewed, and all three show better outcomes in the placebo group. Two of the three had statistically significant differences. These findings suggest that neuroleptics may help suppress symptoms in the short run, but that in the long term they actually impair recovery.

The history of psychiatric treatment of people considered mentally ill is a tragic one, and painful to recount. In mid-eighteenth century England, the first "modern" treatments were established. These included: creating open sores into which caustics would be rubbed daily for months; repeated bleedings to the point of loss of consciousness; liberal use of purges, emetics, "stripes," "blows," restraints, and straight jackets; simulated drowning to the point of unconsciousness; near-starvation diets; and a specially constructed "swinging chair" which could induce vomiting, convulsions, and involuntary urination and defecation (Hunter & Macalpine, 1963; Scull, 1989; Whitaker, 2002). All of these methods were defended by the physicians using them as necessary medical treatments, without which recovery would be impossible. Physicians claimed that insanity was a physical disorder and presented elaborate theories to explain why the insane needed these aggressive physical treatments. The treatments were effective in at least one way: they quickly quieted down unruly and disturbing inmates, making life in the asylum more tolerable in the short term. The long-term effect was to perpetuate both the rational and irrational fears that were actually the primary problem.

For a few decades in the early 1800s, these cruel treatments were replaced by a much more humane approach. Quakers from York, England, decided to create a "retreat" for people in psychospiritual distress when one of their members died from abusive treatment in an asylum. They believed that soft speech, kindness, and comfortable, safe living conditions would best help the insane to recover. About 70% of people provided

these conditions did recover and returned to respectable places in society (Bockhoven, 1972; Scull, 1989). In contrast to the complicated explanations for physical treatments, they stated that they did "little more than to assist nature" in the healing process (Tuke, as cited in Whitaker, 2002). While claims of dramatic successes were common and are best viewed with skepticism, randomized studies of programs similar to moral treatment that have been carried out in the last 30 years have had similar results, without using neuroleptics or other "physical" treatments (Bola & Mosher, 2003; Irwin, in press). The Quakers' approach, which came to be known as "moral treatment," quickly spread to other parts of Europe and to the United States, and by 1840 it had become the dominant system.

When moral treatment was applied on a mass scale, financial limitations caused a steady decline in the quality of the retreats. Some physicians saw an opportunity to reclaim the control that they had lost, and denounced moral treatment as an "unscientific" approach run by "gardeners and farmers" who did not understand the "pathology and treatment of the disease" (Spitzka, as cited in Whitaker, 2002). By 1880, moral treatment had been completely eradicated. Insanity was again labeled a physical disease, and physical treatments were reintroduced. From the 1890s to the 1930s these treatments included: prolonged immersion in very cold or very hot water, which might last days; "needle showers" with jets of pressurized water; "wet packs" where patients were wrapped in wet sheets and left to be squeezed like a vise as they dried; surgeries, such as, hysterectomy, ovariectomy, clitoridectomy, tonsillectomy, colectomy, cholecystectomy, appendectomy, and orchiectomy; injections of various crude glandular extracts; and "deep sleep therapy" where people were kept in a drug-induced sleep for days or weeks at a time. All of these met with initial claims of dramatic cures, but, overall, the patients tended to do poorly (Braslow, 1997; Whitaker, 2002).

During this same period, eugenics became the dominant explanatory model for mental illness, and by the 1920s, American society had accepted the idea that mental illness was genetic in origin. People labeled mentally ill were considered a detriment to society, and to prevent them from breeding they were locked in asylums. Forced sterilization laws were passed, widespread sterilization campaigns were implemented, and there were even calls for euthanasia. The founder of the American Eugenics Society, Madison Grant, wrote an extremely popular book which advocated euthanasia. Grant's book was read by Adolf Hitler, who later ordered the extermination of about 70,000 mental patients before moving the gas chambers to concentration camps in Eastern Europe (Whitaker, 2002).

In the 1930s a new group of treatments became widespread. They quieted people down quickly, and, this time, more often permanently. These included insulin-induced comas, Metrazol—induced convulsions, electroshock, and frontal lobotomy—and they all worked by causing widespread death of brain cells, a fact that was openly admitted at the time based on animal research and postmortem autopsies (Breggin, 1997; Whitaker, 2002). Insulin coma therapy used overdoses of insulin to cause widespread brain cell death. The comas were very deep and repeated as many as 60 times to increase the chances of long-term damage. The person who was once "mad" would become peaceful, quiet, and infantile after such a course. Sometimes these changes were permanent, but more often people gradually returned to their previous state. This was a dangerous treatment with a high mortality rate, so when it was found that a drug, Metrazol, could create powerful seizures that left the patient in a similar state as those given insulin comas, it was readily adopted. While mortality was much lower, as many as 43% of people given a course of Metrazol suffered bone fractures because of the repeated explosive seizures they experienced. When electric shocks were found to

induce similar seizures with less physical damage, electroshock therapy was adopted. Psychiatrists again openly admitted that widespread brain cell death was the main therapeutic measure, and that "the greater the damage, the more likely the remission of psychotic symptoms" (Freeman, as cited in Whitaker, 2002).

The final treatment to gain widespread use before neuroleptics were introduced was frontal lobotomy. This procedure also was hailed as a great breakthrough, and the character changes it caused were usually permanent. By 1950, after nearly 15 years of use, a fairly clear description of its effects emerged in the writings of two of its main proponents, Walter Freeman and James Watts (1950). About 25% of recipients were left completely infantile, often losing their toilet-training ability, another 25% could converse but were, in the words of Freeman and Watts, "at the level of a domestic invalid or a household pet" (p. 190). Among the remaining 50%, those with the very best outcomes could actually perform work, but because of their extreme lack of initiative they were not expected to hold jobs for very long. They also lost any creative imagination or musical ability, no matter how gifted they were prior to the surgery.

In 1954 when the first neuroleptic, chlorpromazine, was introduced, these four treatments were the standard of care in industrialized countries, but it was becoming clear how poor the outcomes actually were. Chlorpromazine was obviously preferable, and was hailed as the next breakthrough even though only a few short-term studies had been performed. When the first long-term results were published about 10 years later, neuroleptics had already become the standard of care, and the negative long-term results were completely ignored.

RESISTANCE TO BIOLOGICAL TREATMENTS

A number of people argued against these physical treatments, and many also have argued against the use of neuroleptics, including some leading psychiatrists. Harry Stack Sullivan, a psychiatrist who founded the journal *Psychiatry* and was editor of the *American Journal of Psychiatry* for many years, wrote in 1940:

> If it were not for the fact that schizophrenics can and do recover; and that some extraordinarily gifted people suffer schizophrenic episodes, I would not feel so bitter about the therapeutic situation in general and the decortication treatments [insulin coma, Metrazol, electroshock, and frontal lobotomy] in particular. (Sullivan, 1940, p. 73)

Sullivan started his career in psychiatry by creating a therapeutic model for people diagnosed with schizophrenia, an interest which continued until his death in 1949 (Sullivan, 1962). He had suffered a psychotic break himself as a young man, and once told a colleague that "he was glad that no electric shock or lobotomy had been prevalent when he was growing up, [because] his case might have been treated so drastically that he would have ended up as a vegetable" (Perry, 1982, p. 3).

Peter Breggin is another well-known psychiatrist who argues against biological treatments. In 1954 he began volunteering in a state mental hospital at the age of eighteen (Breggin, 1991). He has published numerous scientific articles and books critiquing biological psychiatry, and wrote, simply: "There is relatively little evidence that neuroleptics are helpful to the patients themselves, while there is considerable evidence that psychosocial interventions are much better" (Breggin, 1991, p. 67). He has consistently argued that neuroleptics make it much more difficult for people to have a meaningful

recovery, but he cautions against abrupt withdrawal of any psychiatric medications because of the increased risk of drug withdrawal symptoms that often are mistakenly blamed on the person's underlying condition (Breggin & Cohen, 1999).

Loren Mosher pioneered a community alternative to psychiatric hospitalization called Soteria House, when he was the chief of the Center for Schizophrenia at the National Institute for Mental Health in the 1970s. Mosher and Burti (1989) provided a detailed and well-referenced description of how such programs can be organized and implemented. They strongly advocated minimizing the use of neuroleptics:

> We believe that the use of the person interacting with the client is a treatment that can be as powerful as, and have fewer short- and long-term side effects than, the drugs (principally neuroleptics) that are so over-relied on currently. (p. 2)

They also cautioned against abrupt withdrawal of medications, and stated that even with gradual withdrawal some people may not tolerate the potentially severe withdrawal effects.

Bertram Karon is a psychologist with over 30 years of experience doing psychotherapy with nonmedicated schizophrenics. He organized a randomized trial showing that psychotherapy alone, when performed by experienced therapists, was superior to medication alone or combined medication and psychotherapy (Karon & VandenBos, 1981). In a review article on psychotherapy for people diagnosed with schizophrenia, he stated:

> The conclusion that schizophrenic patients must be treated with medication . . . is based on poorly designed studies, the most serious flaw of which is the complete absence of psychotherapists experienced in the treatment of schizophrenic patients by psychotherapy. . . . The optimal treatment for a schizophrenic is psychotherapy, from a competent therapist, without medication, if the patient, therapist, and setting can tolerate it . . . if medication is used it should be seen as a temporary adjunct, to be withdrawn as the patient can tolerate it, and the withdrawal should be a planned part of the treatment. (Karon, 1989, p. 146)

In a 1999 article he sent an even stronger message:

> The real tragedy of schizophrenia is not the severity of the symptoms and the suffering that result for patients and their families. Rather, the real tragedy is that we know of treatments that work but are not using them. Families and patients are settling for treatments that make the patient a lifelong cripple who is not too disturbing. (Karon & Widener, 1999, p. 195)

STUDIES OF LONG-TERM OUTCOMES

All long-term studies of schizophrenia published since 1970 with 12 or more years of follow-up were sought. Studies published prior to 1970 were excluded because of methodological problems as described by Harding, Zubin, and Strauss (1992). They are presented in chronological order by year of publication.

Murphy and Raman (1971)

In 1968, Murphy and Raman (1971) sought out all 90 first-onset schizophrenic patients who had been admitted to Mauritius's Brown-Sequard hospital 12 years earlier. Evaluations were performed by psychiatric nurses through interviews of both the patient

and a person close to him or her to determine the person's current mental state and whether any relapses had occurred in the intervening years. Ninety-eight percent of the patients were available for follow-up.

They found 64% of patients asymptomatic with no psychopathology of any kind. Of these asymptomatic people, 92% had experienced only a single psychotic episode. Patients who were employed at follow-up had a higher mean occupational status than they did prior to their initial hospitalization, and no suicides had occurred. No neuroleptics were used on Mauritius at the time, and only during hospitalization were treatments of any kind offered or forced on people, with 35% of them receiving courses of electroshock and 46% receiving courses of insulin coma.

These outcomes are the most favorable of any of the long-term studies, and yet the patients received no neuroleptics and no outpatient care of any kind. The results are supported by outcomes reported in World Health Organization (WHO) studies, where the course of schizophrenia in over 10 different countries was compared (Hopper & Wanderling, 2000; Jablensky et al., 1992; Leff, Sartorius, Jablensky, Korten, & Ernberg, 1992). Non-industrialized nations, such as Mauritius, had consistently better outcomes in nearly all areas when compared to industrialized nations.

Bleuler (1978)

Manfred Bleuler followed 208 patients prospectively in Zurich, Switzerland, for an average of 23 years. He provided a separate analysis of people who were first admissions: 23% of them had achieved full recovery by his criteria, 43% were significantly improved, and 34% had minimal or no change. Bleuler personally followed these people throughout the follow-up period. Although he did not provide statistical results by treatment, he minimized treatment with neuroleptics and instead emphasized psychosocial approaches. Bleuler's treatment strategy was described by Ciompi (1980):

> He considers that three principles are vitally important. . . . The first consists in therapists relating constantly and actively to the healthy aspects of the psychotic patient. The second concerns the therapeutic effect of sudden and surprising changes in general, social and somatic conditions, often leading to a mobilization of hidden resources. The third consists in calming actions and influences which can be introduced in many ways, the best of them being talking and togetherness, and another being neuroleptic drugs. Bleuler is, however, against a regular, heavy, and prolonged use of such drugs, giving many convincing arguments on the basis of his long-term observations. (p. 419)

Tsuang, Woolson, and Fleming (1979)

Tsuang and colleagues reported on 35-year outcomes for 200 people admitted to an Iowa psychiatric hospital between 1934 and 1944, 93% of whom were evaluated retrospectively. Structured telephone interviews and face-to-face interviews were performed with the person and a first-degree relative.

Twenty percent of the people had little or no psychopathology, 26% had some symptoms but were generally improved, and 54% had severe symptoms. Although these are the worst outcomes in any of the studies reviewed, only 80% of the people studied were first admissions, making it difficult to compare these results to those from other long-term studies. No information on neuroleptic use is provided.

Huber Studies (1975, 1980)

Another retrospective study was done on 502 first admissions diagnosed with schizophrenia in Bonn, Germany (Huber, Gross, & Schuttler, 1975; Huber, Gross, Schuttler, & Linz, 1980). After an average of 22 years, face-to-face interviews were performed and 22% had achieved a complete recovery. Another 43% were classified as recovered with noncharacteristic residual symptoms, leaving only 35% with symptoms characteristic of schizophrenia.

The authors emphasized that the course of schizophrenia was unpredictable. Remissions could happen at any time, even in the second and third decades of illness, and two thirds of the 435 people living in the community, including those with the best outcomes, were not receiving any neuroleptics or other treatments at the time of follow-up.

Ciompi (1980)

Ciompi reported on 289 first admissions who had been diagnosed with schizophrenia in Switzerland an average of 37 years before, and located 96% of them for 2-hour follow-up interviews. Further information was obtained, where available, from family members and hospital files. Twenty-seven percent of the sample had achieved a complete remission and 22% had only residual symptoms.

More than 50% of the people in Ciompi's cohort were diagnosed before 1933 and had never received any "modern" treatments such as insulin coma, electroshock, or neuroleptics, but subgroup analyses showed no significant differences in outcomes by treatment type. Ciompi concluded that these treatments "made no difference at all to the course of the illness" (p. 418), but because few of the people received neuroleptics, he felt that long-term effects of neuroleptics could not be evaluated. Ciompi emphasized that the most important influences on outcomes were: "the expectations of the patient, himself, his family, and surrounding persons which, according to our own recent research, seem often to act strongly as self-fulfilling prophecies" (p. 420).

Ogawa and Colleagues (1987)

In Japan, a prospective study of 140 consecutive patients diagnosed with schizophrenia was carried out, and results were published after 21 to 27 years of follow-up (Ogawa et al., 1987). The entire cohort was part of a "relapse prevention" program emphasizing long-term neuroleptic treatment. Of the 70% of patients evaluated, 31% were considered recovered, 46% improved, and 23% unimproved. The authors defined "recovered" as "without positive schizophrenic symptoms," but did not provide data on how many of these 31% patients still had negative symptoms of schizophrenia. Negative symptoms, which can be incapacitating, include anhedonia (inability to enjoy oneself), flat affect (lack of emotional expression), avolition (lack of initiative), and alogia (inability to speak or defective speech). About 65% of the patients were still taking neuroleptics at follow-up, a much higher rate than reported in other studies. The suicide rate was 11%, which is high even for Japanese standards.

Harding Study (1987) and DeSisto Study (1995)

A group of 180 chronic patients were followed prospectively in Vermont for 32 years. They had originally been diagnosed with schizophrenia using The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, First Edition* (DSM-I) criteria, and in 1987 a reanalysis was published using DSM-III criteria that showed no significant differences in outcomes (Harding, Brooks, Ashikaga, Strauss, & Breier, 1987).

All patients had been part of a special psychosocial program designed for chronic patients who were resistant to treatment. They had been ill for an average of 16 years, continuously hospitalized for 6 years, and on neuroleptics for 2.5 years, before the study began. Two structured interviews were performed, and the authors found that 45% of the patients had no psychiatric symptoms. Another 23% had some psychiatric symptoms but no positive or negative symptoms fitting a diagnosis of schizophrenia.

Regarding treatment, 75% of the patients initially had stated they were taking neuroleptics as prescribed, but by the end of their interviews half of them admitted that they were not taking any neuroleptics. In total, only 25% of the patients were taking medications as prescribed, another 25% were taking them "occasionally," and 50% were not taking any. Unfortunately, no comparison of outcomes by drug status was provided.

This recovery rate is much higher than expected for chronic patients. When compared to a matched control group from Maine, the outcomes for Vermont patients were significantly better in nearly all areas (DeSisto, Harding, McCormick, Ashikaga, & Brooks, 1995). The authors credit the special psychosocial program which emphasized "a pervasive attitude of hope and optimism about human potential, through the vision that, if given the opportunity, persons with mental illness could become self sufficient" (DeSisto et al., p. 340).

Hopper and Wanderling (2000), Harrison and Colleagues (2001)

The WHO's international comparison studies mentioned earlier presented 2- and 5-year outcomes as three separate studies, but were combined at long-term follow-up. Hopper and Wanderling reported 15-year data on a total of 1,223 people in 14 cities from 11 countries, whereas Harrison and colleagues reported on 1,633 people in 18 cities from 14 countries, some for 15 years follow-up and some for 25 years. About 75% of the people were evaluated at long-term follow-up. A more comprehensive description of the findings is to be published in book form (Hopper, Harrison, Aleksander, & Sartiorius, 2004), and four of the centers published individual results. Because all the cohorts used the same standardized outcome measures, a unique opportunity is provided to compare the outcomes in different countries.

Hopper and Wanderling (2000) compared outcomes in "developed" countries to outcomes in "developing" countries. They found that nonindustrialized centers had significantly better outcomes in all areas:

> The finding of a consistent outcome differential favoring "developing" centers is remarkably robust. It extends across all three WHO collaborative projects. It holds for follow-up periods ranging from 2, to 5, to 15 years. It applies when various diagnostic groupings are used. It holds when country groupings shift. It even appears to be relatively constant. (p. 837)

They used a variety of scales to measure recovery. In total, 38% to 48% of all 1,633 people were "recovered" depending on the stringency of the criteria used (Harrison et al., 2001). In nonindustrialized nations, people were two to three times more likely to have good outcomes in all areas and were three to four times more likely to be working. Suicide rates also were higher in industrialized countries, and although exact numbers are not provided, Harrison and colleagues recommended that suicide prevention strategies be considered in industrialized nations.

Reports published by individual centers showed variable results and are difficult to compare. In Sofia, Bulgaria, at 16-year follow-up, 38% had no psychotic symptoms for the last 2 years, which they termed "complete remissions," but only 22% rated "no or minimal" on scales of both symptoms and disability with the remainder having moderate or severe

symptoms (Ganev, Onchev, & Ivanov, 1998). In Nottingham, England, at 13-year follow-up, 44% rated "no or minimal" on scales of symptoms and disability, but only 35% had no positive or negative symptoms of schizophrenia (Mason et al., 1995). In Groningen, Netherlands, at 15-year follow-up, 27% were in "complete remission," meaning that they had no positive ratings on any symptom or disability schedules, and another 17% were living with anxiety or depression, but no symptoms of schizophrenia (Wiersma, Nienhuis, Slooff, & Giel, 1998). In Madras, India, at 10-year follow-up, 66% were "asymptomatic," using two scales which emphasized positive symptoms, but ratings from the global assessment scales used in the other studies were not provided nor was information on other psychiatric symptoms (Thara & Eaton, 1996).

Regarding neuroleptic use in reports from individual centers, the authors from Madras and Groningen did not provide data. In Nottingham, 64% of the people were prescribed neuroleptics at follow-up, but no other data were given (Mason et al., 1995). In Sofia, 65% of the 54 people had been continually prescribed neuroleptics for the preceding 2 years, including 27 of the 32 people who had had continuous psychotic symptoms. Of the 12 people completely off neuroleptics, 10 had had no psychotic symptoms for the preceding 2 years (Ganev et al., 1998). No data were given on compliance rates in any studies.

Data on neuroleptic use was not provided by Harrison and colleagues (2001) nor by Hopper and Wanderling (2000), but at 2-year follow-up it had been found that nonindustrialized nations used them much less (Jablensky et al., 1992). For example, in Agra, India, only 8% of the people were prescribed neuroleptics for more than 45% of the time over the entire 2-year period, compared to 74% in Aarhus, Denmark. Two-year outcomes were much better in Agra, with 63% of the people experiencing complete remission for more than 75% of the time, compared to only 17.5% of the people in Aarhus. Although this difference in neuroleptic use could be partly a result of people needing less medication because they were doing better, it is also likely that economic and cultural factors led to less neuroleptic use in nonindustrialized areas.

The policy in industrialized countries is to impose life-long neuroleptic treatment "to prevent relapse," even when people are asymptomatic. Studies of chlorpromazine reviewed below indicate that people given neuroleptics actually have increased relapse rates compared to people given placebos. This increases the likelihood that reduced neuroleptic use was one of the reasons people in nonindustrialized nations had consistently better outcomes.

Kua, Wong, Kua, and Tsoi (2003)

A 20-year prospective study of 402 people first diagnosed with schizophrenia in Singapore in 1975 was recently published (Kua et al., 2003). Structured interviews were conducted with the people or their primary caregivers periodically, and people were considered to have a good outcome if they had good global assessment scores, were not on treatment, and were working, a condition found in 28% of evaluable people. On a global assessment scale, 44% had either good or excellent levels of functioning. Forty-eight percent were not receiving any neuroleptics, and the 28% of the people considered to have the best outcomes were in this group, by definition, but no other outcomes by treatment status were offered. The authors also documented that 10% of the people committed suicide, a very high rate compared to the general population.

RANDOMIZED TRIALS OF CHLORPROMAZINE VERSUS PLACEBO WITH AT LEAST 1-YEAR FOLLOW-UP

Chlorpromazine was the first neuroleptic introduced and still is considered a benchmark treatment for evaluating newer neuroleptics (Thornley, Adams, & Awad, 2002). The vast majority of chlorpromazine studies, however, have been short-term, as have studies of all other neuroleptics. All available randomized trials of chlorpromazine versus placebo with at least 1-year of follow-up were sought. Studies were excluded if the majority of people had prior exposure to neuroleptics because of the risk of neuroleptic dependency and withdrawal, which tends to bias against placebo (Breggin & Cohen, 1999). Only three studies were found that met these criteria, and they are described in order of publication.

National Institutes of Health (NIH) Collaborative Study Group (1964) and Schooler, Goldberg, Boothe, and Cole (1967)

Although chlorpromazine had been adopted as the treatment of choice many years earlier, the first major trial of chlorpromazine was not published until 1964, with only 6-week outcomes (NIH Collaborative Study Group). Three years later, 1-year follow-up results were published (Schooler et al.). Four hundred sixty-three people newly diagnosed with schizophrenia had been randomized to one of four groups: chlorpromazine, fluphenazine, thioridazine, or placebo. Three hundred forty-four patients completed the study, and 6-week results favored drug treatment over placebo, with no difference between the three drug groups. The drug groups had a high rate of extrapyramidal side effects, with 37% of the chlorpromazine group requiring antiparkinsonian drugs; overall, the authors enthusiastically endorsed neuroleptic use. When the patients were interviewed 1 year later, however, Schooler and associates found that placebo patients had better outcomes with significantly reduced rates of rehospitalization. Although statistically significant, the actual size of the difference is not provided.

Since no other comparisons between placebo and drug groups were reported, and these were the first long-term outcomes ever provided with a placebo-controlled design, the obvious conclusion would be that people diagnosed with schizophrenia did better with minimal exposure to neuroleptics. The authors did not conclude this, however, instead stating: "Because we were unprepared to recommend placebo as treatment of choice, we explored a number of possible variables that might have caused this" (Schooler et al., 1967, p. 991). They gave several possible explanations, but only considered one as being plausible: "When lack of improvement was observed in the patient . . . it may be that the staff responded to the 'deprived' patient with some special quality in care" (p. 994). Although this is a weak and unsupported hypothesis, they accepted it and continued to endorse neuroleptic use.

The authors' endorsement of neuroleptics, despite their negative outcomes, appears to show an obvious bias. Self-serving bias is a basic part of human nature (Dana & Loewenstein, 2003); the entire field of psychiatry would have faced a great loss of self-respect and public influence if chlorpromazine and other neuroleptics actually were causing harm.

There were a number of limitations to this study. At follow-up the reviewers were not blinded, so bias could have affected the results. Given the refusal to accept their negative findings, bias for drug treatment appears most likely. This bias may also explain why more

data on outcomes by treatment group were not published, which is another serious limitation to the study. Finally, patient-derived and family-derived outcome data were not included. The study's major strength is its large sample size, and it remains the largest randomized, double-blind study ever done of chlorpromazine.

Letemendia and Harris (1967)

Letemendia and Harris randomized 28 people diagnosed with chronic schizophrenia to chlorpromazine or placebo in a double-blind crossover design. Although all patients had been hospitalized for at least 5 years, they had no prior history of neuroleptic use. Patients were observed for a total of 2.5 years; all patients began with 6 months on placebo followed by two 9-month crossover periods, and ending with another 6 months of placebo.

There were no statistically significant differences on any outcome measure, but trends consistently favored placebo. The strongest trends occurred with hallucinations and delusions that worsened on chlorpromazine and improved on placebo in both crossover periods. The authors state: "The change in delusions and hallucinations is the opposite of that which is postulated for the action of chlorpromazine on psychosis" (Letemendia & Harris, 1967, p. 955).

This study's strengths were its very long period of direct observation and a very long period of neuroleptic exposure. Its limitations included small sample size, no data on community functioning, lack of patient-derived outcome data, and no information given on prior psychiatric treatments except for the lack of exposure to neuroleptics. The authors note that it had been very difficult to find any patients without prior neuroleptic exposure who were not newly diagnosed with schizophrenia, and that by the time of publication it would have "probably been impossible" (Letemendia & Harris, 1967, p. 950). This shows how widespread neuroleptic use had become by 1967 when the Schooler and colleagues' study (1967) and this study were published.

Rappaport Study (1978)

Rappaport, Hopkins, Hall, Belleza, and Silverman (1978) randomized 80 people diagnosed with schizophrenia to chlorpromazine or placebo using a double-blind design. Patients with minimum prior treatments were included and 74% had zero or one previous hospitalizations. The study was continued until treating teams decided that sufficient improvement had occurred for hospital discharge, which took about 6 weeks, on average. After discharge, the patients were interviewed every 3-6 months for a total of 36 months, but treatments were no longer controlled. The long-term findings, which favor placebo, were obscured by the original authors and misrepresented in an influential review by Wyatt (1991).

There was no statistically significant difference in initial hospital stay, with 42.2 days for chlorpromazine and 45.0 days for placebo patients. At discharge, the chlorpromazine group had a better score on one of the two scales used to measure psychopathology, with no reported differences on the other. After discharge, the authors divided the patients into four groups for statistical analysis: placebo in the hospital and primarily off neuroleptics during follow-up (placebo-off); placebo in the hospital and on neuroleptics during follow-up (placebo-on); chlorpromazine in the hospital and off neuroleptics at follow-up (chlorpromazine-off); and chlorpromazine in the hospital and on neuroleptics at follow-up (chlorpromazine-on). The placebo-off group had the best outcomes on both

scales of psychopathology ($p < 0.001$). The placebo-on group and the chlorpromazine-on groups had the worst scores, with a nonsignificant in favor of the chlorpromazine-on group. Thus the group with the least amount of exposure to neuroleptics, the placebo-off group, had the best outcomes in both of the primary outcome measures.

It is unclear why the authors did not offer a simple comparison of the placebo and chlorpromazine groups. The subgroup data provided by the authors is interesting, but does not answer the basic question set forth by the study which is whether chlorpromazine improves outcomes. This is best answered by comparing the two groups originally randomized to chlorpromazine or placebo. Reanalysis of the authors' data reveals the following: the placebo group as a whole did significantly better on one of the two scales ($p = 0.029$) and had a nonsignificant difference favoring placebo on the other ($p = 0.186$); more placebo patients were off neuroleptics at follow-up (59% vs. 43%, $p = 0.11$); and placebo patients had fewer rehospitalizations (27% vs. 62%, $p < 0.01$). (Statistical calculations provided by the author on request.) Despite these extremely negative findings for chlorpromazine, the authors actually endorse its use, stating that "for most patients diagnosed as schizophrenic, antipsychotic medication is the treatment of choice" (Rappaport et al., 1978, p. 100). They also state that patients who do better without neuroleptics "undoubtedly represent a minority of the schizophrenic population" (p. 109), in contradiction to their own findings.

As occurred in the study by Schooler and colleagues (1967), the authors appear to have revealed a deep-seated underlying bias, which may explain why they reported only subgroup data. If they had reported the overall results, they could not have made the conclusion that only a minority of subjects does better without neuroleptics, and they would also have had to face the uncomfortable conclusion that neuroleptics were making people worse in the long term.

This study has several other limitations. Some patients may have had prior exposure to neuroleptics, which tends to bias against placebo. No information is given on any prior treatments. No patient-derived outcomes were recorded, and there was increased attrition in the placebo group after discharge. The increased attrition in the placebo group would have an uncertain effect. Some studies have actually found that people with the best outcomes are more often lost to follow-up whereas patients with poor outcomes tend to have frequent hospitalizations and increased family requests for outpatient care making them easy to trace. The authors, however, reanalyzed their data "on the assumption that patients lost from the placebo group might also have been those who had the worst scores" (Rappaport et al., 1978, p. 106). After this questionable alteration, the differences still favored placebo, but were no longer statistically significant. One influential review by Wyatt (1991) relied heavily on this reanalysis and even erroneously reported that the placebo recipients lost to follow-up were those with the worst premorbid histories, something not stated or implied anywhere in the study.

DISCUSSION

This review provided three sets of data: a brief history of the physical abuse that was masqueraded as treatment prior to the introduction of neuroleptics; a review of all studies of the long-term course of people diagnosed with schizophrenia, published since 1970 with at least 12 years of follow-up; and, finally, a review of all three randomized, placebo-controlled studies of chlorpromazine in people who had no prior exposure to neuroleptics, with at least 1 year of follow-up.

The history of abusive treatments forced on people labeled as insane reveals what people will resort to in order to suppress truly disturbing behavior. To rationalize these abuses, claims were commonly made that without treatment there was no hope of recovery, and similar claims continued to be made into the early 1990s (Harding & Zahniser, 1994). The review of long-term studies showed, however, that the course of schizophrenia is extremely variable, and that at any given time most people are significantly improved, with 20% to 64% completely asymptomatic.

Comparison of the results of the long-term studies is difficult because of the different outcome measures and assessment criteria that were used, the different lengths of follow-up, and changes in the definition of schizophrenia over the past 80 years. Caution is needed in evaluating rates of recovery, as exemplified by the case of frontal lobotomy where success was claimed despite tragically poor outcomes. The best comparison of these long-term studies probably comes from comparing the percentage of patients with no psychiatric symptoms, which ranged from 20% (Tsuang, Woolson, & Fleming, 1979) to 64% (Murphy & Raman, 1971). Murphy and Raman's patients also had the most favorable course reported, with 59% having a single psychotic episode followed by complete remission, and no suicides. No neuroleptics were used, suggesting that neuroleptics are unnecessary and may actually inhibit recovery. This finding is supported by studies in other nonindustrialized nations where neuroleptics were used less often but outcomes were significantly better than in industrialized nations (Hopper & Wanderling, 2000; Jablensky et al., 1992). In industrialized countries, the recovery rate was exactly the same (27%) for people diagnosed in the early 1900s (Ciompi, 1980) as for those diagnosed in the 1980s (Wiersma et al., 1998). This suggests that even recently introduced neuroleptics offer no improvement over the physical abuses used at that time.

Only three placebo-controlled studies of chlorpromazine for people with no prior neuroleptic exposure were found that had at least a 1-year follow-up. All three studies found that long-term results were better in the placebo group, with statistically significant differences in two of the three. These same two studies found that the drug group did better at 6 weeks, but the opposite was true at long-term follow-up (Rappaport et al., 1978; Schooler et al., 1967). The authors resisted their negative findings, in one case by creating an implausible hypothesis and in the other by only publishing subgroup data, and continued to endorse neuroleptic use despite their negative outcomes.

Two prior reviews concluded that chlorpromazine was more effective than placebo (Thornley et al., 2002; Wyatt, 1991). Those reviews included many of the studies excluded from this one, including drug-withdrawal studies and studies with no placebo control, such as, Simon, Wirt, Wirt, and Halloran (1965). Thornley and associates (2002) excluded direct chlorpromazine-withdrawal studies, but included studies with withdrawal from other neuroleptics. Wyatt reviewed neuroleptic studies, in general, not only chlorpromazine studies, but showed obvious biases and misrepresented data regarding Rappaport and colleagues (1978) by stating erroneously that patients with the worst histories in the placebo group were lost to follow-up. He concluded that withholding neuroleptics was "biologically toxic" to the brain (p. 347), but completely ignored widely recognized brain damage caused by neuroleptics in the form of tardive dyskinesia (TD), an often permanent and grossly disfiguring movement disorder. Several years before Wyatt's review, the American Psychiatric Association had stated that neuroleptics could cause TD in up to 40% of people who took them for 5 years or more (Karon, 1989). Some studies of the prevalence of TD have actually found that the rate has increased in the past 20 years, from 20% in 1981 to 43% in 2000, despite the introduction of newer neuroleptics (Halliday et al., 2002).

The finding that chlorpromazine worsens long-term outcomes raises questions about newer "atypical" neuroleptics, such as, risperidone (Risperdal), olanzapine (Zyprexa), and quetiapine (Seroquel). Many people believe that they are safer and more effective than older neuroleptics, but the Food and Drug Administration (FDA) specifically forbade any claims to this effect because the studies submitted to the FDA were biased by design (Whitaker, 2002). Studies performed after the drugs came onto the market have confirmed the FDA's suspicions. For example, risperidone, initially claimed to have minimal extrapyramidal effects, later was found in several studies to cause more extrapyramidal effects and other adverse effects than older neuroleptics (Knable, 1997; Rosebush, 1999; Sweeney, 1997). Although there is agreement that atypical neuroleptics cause less TD, it takes time for long-term adverse effects to be uncovered. A recent meta-analysis concluded that there was no reliable evidence that atypical neuroleptics are more effective or better tolerated than older neuroleptics, such as chlorpromazine (Geddes, Freemantle, Harrison, & Bebbington, 2000). Makers of the new drugs were allowed to claim effectiveness over placebo, but the FDA allowed drug-withdrawal studies to be used for this claim. All of the studies sent for FDA approval started with chronic patients already taking neuroleptics who were then abruptly withdrawn before being assigned to placebo or neuroleptic treatment. This allowed rapid recruitment of actively psychotic patients, but created a built-in bias against placebo (Whitaker, 2002).

Claims that neuroleptics prevent relapse also came from drug-withdrawal studies that ignored several biases including drug withdrawal effects, biased samples, and penetration of the double blind. Abrupt withdrawal triples the relapse rate when compared to gradual withdrawal, and most studies of relapse used abrupt withdrawal (Baldessarini, 1995). Biased samples were created because only the small minority of people who were stable on neuroleptics for over a year was included in the drug-withdrawal studies. Another potential bias in all double-blind studies is that it is relatively easy for patients and staff to penetrate the double-blind. As many as 100% of patients experiencing side effects are able to correctly guess that they are receiving the active medication (Antonuccio, Danton, DeNelsky, Greenberg, & Gordon, 1999; Fisher & Greenberg, 1993).

A number of factors have been proposed to explain the improved outcomes in nonindustrialized nations, including supportive kin, different belief systems, forgiving social environments, and different work environments. The two factors considered by this author to be most significant, in addition to the reduced use of neuroleptics, are different beliefs and work environments. In nonindustrialized nations, the people must work to survive, whereas in industrialized nations long-term "disability" usually qualifies people for benefits allowing them to live at a low socioeconomic level without working. When economic reality forces people to work, as occurs more often in nonindustrialized countries, they may have higher social status, more social interaction, and improved feelings of self-worth than people who are essentially wards of the state. If people on long-term disability "recover," they will lose their benefits, so they are actually encouraged to keep their label. The belief system still prevalent in industrialized nations is that schizophrenia is a lifelong illness requiring lifelong drug treatment. The negative belief system generated by the eugenics movement, that people diagnosed with schizophrenia have defective genes, still predominates, as does the belief that one's genetic core is unchangeable. Several long-term study authors pointed out that expectations of the person and people around them may have significant influence, and belief in eugenics encourages extremely low expectations.

There are several explanations for why neuroleptics may worsen long-term outcomes. People exposed to neuroleptics and other drugs naturally adapt their physiology through alterations in receptor number and function. These changes create physiological dependency which reinforces psychological dependency. The current heavy emphasis on drug treatment may also allow underlying social, psychological, and spiritual issues to remain unaddressed. All of these factors could combine to worsen outcomes, especially since most people do not tolerate the often severe adverse effects of neuroleptics and so choose not to take them unless forced to do so.

Although there may be individuals who do better with drug treatment, they, at best, represent a minority. People who wish to attempt drug treatment should be warned of the possibility of worse long-term outcomes, increased relapse rates, drug withdrawal symptoms, and other adverse effects. They also should be warned that the belief that neuroleptics are safe and effective is based on studies with biased reporting and biased study designs. All treatments should be voluntary, including psychosocially based treatment programs, and based on informed consent. If someone has broken a law, they should be treated the same as other people who break laws. Neuroleptic treatment should not be offered as an alternative to taking responsibility for one's actions and should not be forced.

It may be difficult for many people to understand how neuroleptics could be so widely promoted and used when the available research suggests that they worsen long-term outcomes. The history of preneuroleptic treatments was offered to demonstrate that treatment choices for people in severe psychospiritual distress have never supported long-term recovery. More likely, they were designed as a defense against the disturbing nature of psychosis, with short-term suppression of symptoms as the major goal; the same is true of neuroleptics. The alternative, to face one's fears by trying to understand and support people experiencing psychosis, is extremely challenging, but, ultimately, much more rewarding.

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