RESEARCH ON THE DRUG TREATMENT OF SCHIZOPHRENIA: A CRITICAL APPRAISAL AND IMPLICATIONS FOR SOCIAL WORK EDUCATION

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Social work authors have presented superficial appraisals of atypical neuroleptic (antipsychotic) drugs used to treat schizophrenia. This article presents a critical overview of clinical trials and research strategies involving conventional and atypical drugs. It identifies 14 distinct methodological and conceptual failings and neglected research directions. These flaws raise serious doubts about the scientific justifications for the widespread use of neuroleptics. Implications for a critical social work education stance about psychopharmacology are discussed. Findings from psychopharmacotherapy studies cannot be taken at face value: social work educators must scrutinize the adherence of the research enterprise to the scientific method and situate its findings in their historical, ideological, and political-economic contexts.

SCHIZOPHRENIA IS CONSIDERED the epitome of severe and persistent mental disorder and remains the focus of considerable research activity, mostly about its psychopharmacological treatment. The introduction of neuroleptic (antipsychotic) drugs in the 1950s launched a biological revolution in psychiatry and profoundly altered the treatment of schizophrenic disorders. By the mid-1980s, however, professionals could no longer avoid recognizing the drugs' significant drawbacks. Antipsychotics cause movement disorders (extrapyramidal symptoms, EPS) in acute treatment which often become irreversible in long-term treatment. They cause or worsen negative symptoms, such as apathy and psychomotor retardation. Antipsychotics are ineffective in short-term treatment to suppress psychotic symptoms and in long-term treatment to prevent relapses in at least a substantial minority of patients (Cohen, 1997a). By 1986, the physician credited with introducing them in psychiatry asked, "Are the antipsychotics to be withdrawn?" (Deniker, 1986).

The tide began to shift following the widely heralded reintroduction of clozapine into common use in 1990, when older neuroleptics began to be called "typical," "conventional," or "classical" in their propensity to cause movement disorders. Clozapine was "atypical" in that it did not cause profound catalepsy in rats (the animal model of neuroleptic-induced parkinsonism in humans), and seemed to manifest a broader spectrum of biochemical actions. Since then, other neuroleptics referred to as "atypical" have been marketed in the United

Journal of Social Work Education Vol. 38, No. 2 (Spring/Summer 2002).

States. These include risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), sertindole (later withdrawn from the market), and ziprasidone (Geodon). These newer drugs have ushered what one social work author describes as "great optimism and expectation today in the psychopharmacotherapy of schizophrenia" (Bentley, 1998, p. 387). The social work literature on these drugs has echoed in nature the claims made for the newer drugs by psychiatrists. For example, in a textbook on social work intervention in mental health, Sands (2001) states that "'Atypical antipsychotics'. . . treat the negative as well as the positive symptoms of schizophrenia and have fewer side effects than their predecessors" (p. 296). In an article on "What Social Workers Need to Know" about psychopharmacological treatment of schizophrenia, Bentley (1998) states, "The newer neuroleptics are called atypical specifically because they are not associated with EPS. . ." (p. 389). In a textbook on clinical social work and medications (Austrian, 2000), the chapter by Hird (2000), a physician, concurs: "Now, a number of new 'atypical' antipsychotics are more effective in treating the negative' symptoms without introducing the severe side effects of the earlier antipsychotic medications" (p. 284). Although these benefits would, in effect, constitute a veritable revolution in the field of schizophrenia treatment, the articles in which these statements appear do not provide the authors' rationales for arriving at their judgments. The judgments merely seem to echo the supportive descriptions of atypicals in scores of psychiatric journal articles.

Supportive statements notwithstanding, evidence has existed since the arrival of atypicals to illustrate what has been a recurring pattern in psychiatry: as an older treatment falls into disrepute, the benefits of a newer treatment are overstated (Cohen, 1994). There are now scores of reports of EPS such as *severe* dyskinesias and dystonias (e.g., Ahmed et al., 1999), *severe* akathisia (e.g., Jauss et al., 1998), neuroleptic malignant syndrome (Al-Waneen, 2000; Karagianis, Phillips, Hogan, & LeDrew, 1999; Stanfield & Privette, 2000), as well as tardive dyskinesia (TD) (e.g., Ananth & Kenan, 1999; Spivak & Smart, 2000) associated with nearly every atypical drug on the market. In a 2000 study by Modestin, Stephan, Erni, and Umari of 200 patients treated for several years with older neuroleptics or with clozapine, the authors conclude: "On the whole, long-term relatively extensive use of clozapine has not markedly reduced the prevalence of extrapyramidal syndromes in our psychiatric inpatient population. In particular, we failed to demonstrate a beneficial effect of clozapine on prevalence of TD" (p. 223). As to the unique therapeutic profile of the newer drugs, the authors of a meta-analysis of 52 randomized controlled trials with 12,649 subjects (Geddes, Freemantle, Harrison, & Bebbington, 2000) comparing six atypical antipsychotics with conventional ones (usually haloperidol or chlorpromazine), concluded,

> There is no clear evidence that atypical antipsychotics are more effective or are better tolerated than conventional antipsychotics [and further], many of the perceived benefits of atypical antipsychotics are really *due to excessive*

> *doses of the comparator drug used in the trials* [italics added]. . . . Overall, no evidence was identified to suggest that any individual atypical antipsychotic had a specific effect on either positive or negative symptoms. (p. 1375)

Evidence conflicting with a prevailing consensus must be critically evaluated and contrasted with the weight of other evidence, and more definitive judgments must await the integration of future findings. However, a more critical stance regarding the positive claims being made for the atypical neuroleptics is necessary for several reasons, only two of which need to be mentioned in this introduction. First, the enterprise of medicating schizophrenia was characterized for nearly three decades by the mass production of *obvious* treatment-induced disease, accompanied nonetheless by mass professional denial that such iatrogenesis was occurring (see, among others, Brown & Funk, 1986; Cohen, 1997b; Gelman, 1999; Whitaker, 2001). Second, the "claims being made for the newer atypical compounds. . . take place in the context of ever greater conflicts of interest, both academic and monetary" ("Drug Treatments," 1999, p. 4.). (See also Bodenheimer, 2000; "The Tightening Grip," 2001.) For these and other reasons, data that question popular notions about the nature or benefits of new antipsychotics need to be carefully considered before social workers consider the newer drugs as distinct improvements. Such a critical analysis especially behooves members of a mature and scientific helping profession with ubiquitous involvement in mental health. As a contribution to the independent social work assessment of psychotropic drug effects, this paper presents a critical analysis of studies of the drug treatment of schizophrenia. It then discusses various implications of this analysis for thinking and teaching about psychotropic drugs and psychopharmacology in social work.

Critical Overview

The approach of the following analysis consists of identifying and describing mainly methodological and conceptual failings and limitations of randomized controlled trials (RCTs) and other clinical studies of the effectiveness of neuroleptic drugs in the treatment of schizophrenic disorders. RCTs carry substantial scientific weight: they are considered the "gold standard" design to test effectiveness in reducing the symptoms of various conditions, and to a lesser but extremely important degree, to determine whether various positive or adverse effects observed in association with drug treatment should be properly attributed to the drugs. The need for a critical review focusing on methodological issues in clinical trials is underscored by two concerns. First, the quality of controlled schizophrenia trials, as measured by clear reporting and clinical applicability, is uniformly poor and has not increased in decades (Thornley & Adams, 1998, see below), and there is some evidence that it has actually declined (Ahmed, Soares, Seifas, & Adams, 1998). Second, Geddes et al.'s (2000) previously cited conclusion to their meta-analysis explicitly points to a deliberate confounding methodological factor—high doses of conventional antipsychotics used in RCTs testing the effectiveness of atypical

antipsychotics—to account for many perceived benefits of the latter drugs.

Failure to Determine Sample Sizes Appropriately

The aim of an RCT should be to test a hypothesis, for example, that a given drug is superior to a placebo or to another drug in improving the mental state of patients with a given diagnosis. The accuracy with which we can detect a statistically significant difference between treatment and control group depends on sample size. To minimize the likelihood of Type I and Type II errors, one increases sample size or effect size; this is the statistical power of the study, determined by a simple formula (Elwood, 1998).

Thornley and Adams (1998) performed a meta-analysis of 2000 controlled trials of the treatment of schizophrenia—86% of which evaluated the effects of 437 different drugs—published between 1948 and 1997. The average number of trial participants was 65, with no discernible change over time. Only 1% raised the issue of the statistical power of the study, and only 3% had enough subjects (n=150) in each treatment arm to show a 20% difference in improvement in mental state between groups.

Failure to Report Methodology Properly

In Thornley and Adams' (1998) meta-analysis, a mere 1% of the 2000 trials achieved a maximum quality score of five points assigned by the authors. Two thirds of the trials scored two points or less, which means that "they barely, if at all" (p. 1182) described attempts to reduce bias at assignment or rating of outcome, placebo effects, or the fate of participants. Quality of reporting did not improve with time: from 1950 to 1997 the mean quality score remained under 2.5. From meta-analyses of other treatments, Thornley and Adams deduce that the poorer the quality of reporting, the higher the estimates of benefits of the tested treatment. They conclude, "schizophrenia trials may well have consistently overestimated the effects of experimental interventions" (p. 1183).

Failure to Control for Penetration of the Double-Blind

A principal source of bias in clinical trials is that investigators' expectations can influence their evaluations in ways that alter the outcomes (Smith, 1989). For this reason, many RCTs use procedures to make clinicians and patients unaware of which patient receives which treatment ("double blind"). However, Fisher and Greenberg (1993) argued that the use of comparison drugs with obvious adverse effects contributes to "unblinding" clinical trials, revealing to clinicians and patients who is receiving active drugs or placebo.

In the vast majority of recent antipsychotic drug trials, especially involving atypicals, the comparison drug used is haloperidol (Haldol), long considered the "gold standard" antipsychotic. But how does haloperidol routinely affect cognition and behavior? Ramaekers et al. (1999) summarized this drug's effects on 21 healthy volunteers who received four milligrams daily for merely five days: "Haloperidol ubiquitously impaired psychomotor and cognitive performance. . . . It produced extrapyramidal disturbances in nearly every subject, the most common being

akathisia. . . . [H]aloperidol produced a number of mental disturbances, the most noteworthy being negative symptoms" (p. 209). Obviously, as Thornley and Adams (1998) remarked in connection with the use of haloperidol in clinical trials in general, "This drug is likely to give obvious side effects that render successful blinding difficult, if not impossible. . . ." (p. 1183). Despite such observations, extremely few studies report *how* observers are kept blind about treatment conditions, and fewer still report results of *testing* for blindability (e.g., by asking clinicians or patients to guess who is receiving the active drug or the placebo).

Failure to Control for Neuroleptic Residue in the Body

Many drug treatment studies use a "crossover" design, where subjects are randomly assigned to treatment and control groups but switch groups at some point in time. Measurements are taken at the end of each phase. Perhaps the chief limitation of this design is that residual effects of treatment—beneficial and adverse—may persist after patients switch from one group to the other, leading to contamination of the next phase (Fleming, 2000). To minimize this, some studies might include a "washout period" (usually one week) between changes. Is this time interval sufficient to eliminate drug residue before patients are switched to placebo or other drugs?

In a rat, traces of a *single* small dose of haloperidol can be detected 180 days after administration (Cohen, Herschel, Miller, Mayberg, & Baldessarini, 1980). The average half-life of haloperidol (the time it takes for half of a drug's quantity to be excreted) from human brain tissue was calculated to be 6.8 days (Kornhuber et al., 1999). Such findings suggest that patients exposed to haloperidol are unlikely to be free of its residual effects for several weeks, and perhaps for several months, after withdrawal. Thus, the effects of the subsequent treatment or "drug-free" period are contaminated.

Failure to Scrutinize Assertions That Atypicals Appear to Cause EPS No More Often Than Placebo

The statement in this section's title is taken from an advertisement for risperidone appearing in the April 1994 issue of the *American Journal of Psychiatry*, stating, "incidence and severity of extrapyramidal symptoms (EPS) were similar to placebo" (p. A11). Similarly, an ad for quetiapine appearing in the March 2002 issue of the same journal states that this antipsychotic has "an EPS profile *no different than placebo* [italics in original]" (p. A23). Sometimes authors themselves have stated flatly that "[atypicals] do not cause extrapyramidal side-effects" (Kendrick, 1999, p. 745)—which is false. At best, atypicals have a lower, as yet undetermined, propensity to cause EPS. Still, the assertion of equivalence with placebo undoubtedly conveys the message that such drugs are virtually *harmless*. What does it rest on? It rests on published findings from several short-term studies comparing one group of haloperidol-treated patients switched to placebo, with another group of haloperidol-treated patients switched to an atypical neuroleptic. In the first group, one would expect to see a moderate rate of withdrawal-emergent EPS within the first few

weeks (as extrapyramidal symptoms regularly emerge or exacerbate at least temporarily when the dose of an antipsychotic is reduced or withdrawn). In the studies discussed, because patients are switched to placebo, this rate becomes the "placebo incidence" of EPS! And this withdrawal-emergent rate is compared to the incidence of EPS observed in patients switched to a different antipsychotic, which is expected to have a masking effect on EPS, as most antipsychotics do.

The best that one can say about such studies is not that they show atypicals to produce EPS no more often than placebo, but that *atypicals seem no better than placebo at managing withdrawal from haloperidol.* In this author's view, both the existence and the continued acceptance (by manuscript reviewers, journal editors, regulatory agencies) of such a deliberately misleading design, one which incorporates such a predictable confound, raises extremely serious questions about the scientific quality of the enterprise.

Failure to Report Patients' Post-Treatment Ratings

Standard procedure in RCTs suggests that "Post-treatment evaluations should be continued weekly for up to four weeks" (Irwin & Singer, 1988, p. 369). As we have seen above, this short period probably ignores the confound of neuroleptic residue. However, the principle of rating patients after treatment remains profoundly important because such ratings provide perspectives on drug effects when participants are no longer under the drug's influence. Jacobs and Cohen (1999) have argued that the evaluation of a psychotropic substance is *always* incomplete until the user has had a chance to look back upon the drug-taking experience from a drug-free standpoint.

Healy and Farquhar (1998) provide a dramatic illustration of how relevant the post-treatment perspective can be. In their study, 18 of 20 normal volunteers having taken a single dose of the antipsychotic droperidol reported no undue discomfort whatsoever when questioned during testing a few hours after ingestion. However, when brought back for follow-up evaluation two weeks later, all these subjects reported having been under "extreme distress," that "even when they were denying discomfort they had been acutely restless, impatient or dysphoric" (p. 116). Apparently, while under the drug's influence, subjects were simply unable or unwilling to admit to this intensely altered, dysfunctional state.

Post-treatment ratings by participants in clinical trials and other treatment studies are rarely, if ever, reported. Researchers thus cannot compare ratings made at different times and analyze potential discrepancies between them. Yet, such discrepancies constitute possibly the most valuable means to understand the actual psychological alterations produced by psychotropic drugs as well as subjects' accommodations to these alterations (Jacobs & Cohen, 1999).

Failure to Consider Social Functioning as an Outcome Measure

Schizophrenia refers to a persistent mental disorder with serious cognitive, interpersonal, vocational, and social impairments. Of 2000 controlled schizophrenia trials, how-

ever, a mere 6% evaluated social functioning while 81% evaluated psychiatric symptoms or behavior (Thornley & Adams, 1998). Given that over 90% of participants in these trials, even during the last decade, were *hospitalized* patients (and mostly American or British), findings cannot be generalized to the vast majority of individuals diagnosed with schizophrenia. Until measures of social and vocational functioning are carefully integrated into clinical trials, such trials cannot provide meaningful information about the real-life "effectiveness" of neuroleptics on domains besides acute symptom exacerbation.

This point has long been recognized (e.g., Barnes, Milavic, Curson, & Platt, 1983; Diamond, 1985) but has not sufficiently influenced the design of contemporary drug trials, even of atypicals, which are sometimes touted as fitting well with the era of community treatment. For example, in a meta-analysis of all 30 available RCTs comparing clozapine with conventional neuroleptics, Wahlbeck, Cheine, Essali, and Adams (1999) observed a clinical advantage for clozapine, and even that patients were more satisfied with their treatment, but noted, "there was no evidence that the superior clinical effect of clozapine is reflected in levels of functioning; on the other hand, global functioning and pragmatic outcomes were frequently not reported" (p. 990).

Failure to Consider the Impact of Abrupt Drug Withdrawal

Researchers and clinicians have long noted that after patients stop taking their neuroleptic medication, a good proportion of them seem to suffer a "relapse" (exacerbation of psychotic symptoms). However, patients might stop their medication—or have it stopped—gradually or abruptly. How abrupt is abrupt withdrawal? Gilbert, Harris, McAdams, and Jeste (1995) located and reviewed 66 studies specifically reporting outcomes after neuroleptic drugs were withdrawn from schizophrenic patients. In over two thirds of the studies providing appropriate details, whether the drug treatment had lasted for weeks, months, or years, it usually "was withdrawn acutely over 1 day" (p. 175)! Re-analyzing Gilbert et al.'s data, Baldessarini and Viguera (1995) found that among abruptly withdrawn patients (duration of two weeks or less) the relapse rate was *three times greater* than among more gradually withdrawn patients. This confirms that abrupt withdrawal constitutes a powerful confound in drug research because it artificially inflates the relapse rate, thus making indefinite or maintenance neuroleptic treatment seem much more attractive. This author has previously argued (Cohen, 1997a) that without this confound, maintenance treatment might be seen to confer *no additional advantage over gradual drug withdrawal*, and, given the obvious risks such treatment poses, might actually appear unjustifiable.

Failure To Distinguish Between "Relapse" and "Withdrawal-Induced Psychosis"

Closely related to the previous point, this issue has been raised explicitly by Cohen (2001). Withdrawal or discontinuation syndromes should normally be expected whenever drugs that significantly alter brain function—and trigger changes in neurochemistry as the brain adapts to this alteration—

are abruptly withdrawn. Besides obvious motor disorders, discontinuation syndromes have been outlined since the 1960s in studies of neuroleptic treatment of psychotic, non-psychotic, and non-psychiatric conditions. Nevertheless, systematic investigation of withdrawal syndromes has been thoroughly neglected (Breggin & Cohen, 2000; Tranter & Healy, 1998). Syndromes following lithium, antidepressant, and benzodiazepine withdrawal have been recognized as true withdrawal effects that often *frankly mimic* the symptoms for which the drug was originally prescribed (Goodwin, 1994; Schatzberg et al., 1997). Do observed reactions following drug withdrawal constitute a reemergence of psychiatric symptoms indicating the need for continued treatment, or "discontinuation-associated iatrogenic risk" (Suppes, Baldessarini, Faedda, Tondo, & Tohen, 1993, p. 131) indicating the need for less abrupt withdrawal?

Since Ekblom, Eriksson, and Lindstrom's (1984) early description of two cases of rapid-onset (24–48 hours), very pronounced psychosis following abrupt clozapine withdrawal, several virtually identical reports of rapid-onset, "supersensitivity" withdrawal psychosis with serious deterioration have been published—especially involving atypical neuroleptics and quick disappearance of symptoms upon reinstituting the drug (e.g., Berecz et al., 2000; Durst, Teitelbaum, Katz, & Knobler, 1999; Llorca, Vaiva, & Lancon, 2001). In one RCT, Tollefson and colleagues (1999) observed 25% of patients abruptly withdrawn from clozapine and switched to placebo for only three to five days develop the following "core symptoms": "delusions, hallucinations, hostility, and paranoid reactions" (p. 435).

Given the above lines of evidence, it is legitimate to wonder how rapid-onset psychoses following neuroleptic withdrawal or cessation might be defined in numerous research projects, not to mention ordinary clinical settings. This author believes that these psychoses are called "relapses," are attributed to patients' psychiatric conditions, and are seen as confirmation that neuroleptics are "effective" and that their use must continue indefinitely. Do these psychoses point to neuroleptics' effectiveness or neuroleptics' toxicity? We will not know until researchers decide to test the sound hypothesis that they are true withdrawal syndromes which would abate with gradual taper (Cohen, 2001).

Failure to Conduct Systematic Studies of Gradual, Patient-Centered and Patient-Directed Drug Withdrawal

Although theoretical, clinical, practical, and ethical justifications for discontinuing or withdrawing neuroleptic drug treatment abound, and although the issue of withdrawal has enormous importance for consumers, rational drug withdrawal may be the least studied topic in clinical psychopharmacology and the one about which clinicians are most ignorant (Breggin & Cohen, 2000). In a 9-line algorithm for "treatment-refractory schizophrenia," trying a drug-free period is relegated to lines 8 and 9, after augmentation strategies (adding drugs such as lithium), "very high doses" of neuroleptics, electroconvulsive therapy, and the use of "investigational compounds" (Koshino, 1999).

There are many ways to conduct a study to investigate the potential advantages of neuroleptic withdrawal and substitution with non-drug supports. For example, one might select patients (and families) who strongly desire it, educate them about effects to anticipate, help them set up peer and professional support networks, proceed with a very gradual taper (e.g., approximately 10% of the dose reduced every month or two) and adjust its speed based on patients' regular feedback, introduce flexible psychosocial supports (in the form of a personal assistant as proposed by the independent living movement for disabled persons, for example), complement with changes in nutrition and exercise, rehearse cognitive and behavioral strategies for symptom reduction, and avoid major social, vocational, and residential changes during the first few months of the program (as the risk of relapse following drug withdrawal seems non-linearly distributed, with excess risk mostly occurring during the first 12 weeks). (See Breggin & Cohen, 2000.) Despite the hundreds of different interventions that have been tested for schizophrenia, this author is not aware of a single such study in nearly 50 years of neuroleptic therapy. However, a few studies even falling far short of this ideal have yielded positive results (e.g., Liberman et al., 1994). Also, the passage of the Nursing Home Reform Act (part of the Omnibus Bill Reconciliation Act of 1987, or PL 100-203) mandated yearly reviews of the drug regimens of institutionalized dependents in nursing homes and in institutions for the developmentally disabled as a condition of continued federal funding. As a result, systematic neuroleptic dose reductions or withdrawals have been conducted in many establishments. To date, published evaluations of such withdrawal programs have been consistently positive (e.g., Thapa, Meador, Gideon, Fought, & Ray, 1994).

Failure to Study Polypharmacy

Treatment of schizophrenic patients with a single drug is the exception rather than the rule. In Western countries, these patients often simultaneously receive more than one neuroleptic as well as various other central nervous system depressants such as benzodiazepines, lithium, anticonvulsants, and antiparkinsonians (Fourrier et al., 2000; Tognoni, 1999). With the advent of managed care in the United States, pressures to decrease length of hospital stay are correlated with increases in the number of patients receiving drugs and in the number of drugs prescribed during an acute hospitalization (Baldessarini, Kando, & Centorinno, 1995). Polypharmacy was previously declared irrational but the arrival of new antipsychotics has provided fresh justifications for the practice (Canales, Olsen, Miller, & Crismon, 1999). Barely understood but clinically significant interactions occur with all agents commonly used in conjunction with neuroleptics (Zumbrunnen & Jann, 1998). Furthermore, most schizophrenic patients smoke heavily, and nicotine is known to decrease blood levels of many neuroleptics (Kelly & McCreadie, 1999). The portrait is further complicated by occasional findings that benzodiazepines are comparable in effectiveness to conventional neuroleptics in the 4-week symptomatic treatment of psychosis (Carpenter, Buchanan, Kirkpatrick, & Breier, 1999).

Despite the preceding points, published systematic evaluations of polydrug regimens are virtually nonexistent. Yet, given the complex chemical cocktails patients routinely ingest, often for years, it may be illusory to attribute any perceived benefits to one particular class of drugs in the cocktail. Furthermore, given that a small proportion of schizophrenic patients—probably less than one fifth—take only a single drug, it is irresponsible to justify the long-term polydrug treatment of schizophrenia by means of studies investigating the relatively short-term administration of a single drug.

Failure To Distinguish Between "Noncompliance" And "Nonresponse"

Many discussions of the effectiveness of antipsychotic drugs assert that patients' "noncompliance" (defined as refusal or inability to take medication as prescribed because of its unpleasant effects or patients' "lack of insight") largely accounts for high relapse rates in schizophrenia. Relapse is often attributed to noncompliance despite a one-year relapse rate of 40% in patients who *take* their medication, compared with a 65% relapse rate for patients on placebo (Hogarty & Ulrich, 1998). Interestingly, rates of noncompliance, typically 35% to 50% of patients, are similar to rates of "nonresponse," that is, an observer's judgment that the treatment fails to elicit the desired response (e.g., the patient shows no change, worsens, or develops intolerable adverse effects).

Despite widespread clinical evidence of nonresponse to neuroleptics, it is fair to say that no discussion of this phenomenon existed in the entire medical literature until the arrival in the United States of clozapine, marketed specifically for the treatment of "neuroleptic non-responsive patients." Nonresponse to neuroleptic drugs is commonly observed even during short-term treatment when simply suppressing behavior and rendering the patient passive will rate as improvement over a state of psychotic agitation; in studies reviewed by Cohen (1997a), up to two thirds of patients in eight-week long neuroleptic trials are rated as non-responders even after dose changes or drug switches. For these reasons, the following hypothesis deserves investigation: in the multifactorial process that leads patients to take or not take variably effective medication that invariably produces unpleasant effects, but is nevertheless viewed by most professionals as *the* essential component of schizophrenia treatment, these professionals are likely to interpret or translate nonresponse as noncompliance.

Insufficient Study of Neuroleptic-Induced Dysphoria

In addition to, or closely related to the emergence of EPS, neuroleptics induce negative subjective reactions usually termed dysphoria or mental side-effects (Gerlach & Larsen, 1999). This is probably the most frequently-voiced complaint by patients who take neuroleptics. Yet, despite evidence linking dysphoria to "poor treatment outcome" and "noncompliance" weeks and months later (Awad & Hogan, 1994), this area of research has been seriously neglected in the contemporary literature. Wallace (1994), summarizing topics discussed by thousands of callers to SANELINE (a telephone helpline in the U.K. for people diagnosed or coping with

severe mental disorders), writes the following of callers who worry about medication:

> Almost all of our callers report sensations of being separated from the outside world by a glass screen, that their senses are numbed, their willpower drained and their lives meaningless. It is these insidious effects that appear to trouble our callers much more than the dramatic physical ones, such as muscular spasms. (pp. 34-35)

It is no exaggeration to state that such an observation might never appear in the published report of a modern clinical trial. Nor would we exaggerate to assert that despite a drug-treated patient showing "improvement" according to reductions in scores on a psychiatric symptom assessment scale, that patient might still feel, plainly, miserable.

Insufficient Study of Neuroleptic-Induced Neuropathology

Searching the Medline database for reviews of neuroleptic-induced neuropathology (drug-induced changes in the structure of brain cells) published between 1996 and 2000, this author located only two such articles (Harrison, 1999; Jeste, Lohr, Eastman, Rockwell, & Caligiuri, 1999), compared to nearly two dozen on the neuropathology of *schizophrenia*. Although various subtle and not-so-subtle anatomical changes are regularly observed in the brains of a minority of schizophrenic patients, the neurotoxic effects of drugs loom large as causative or contributing factors. During the last five years only, a dozen studies have reported neuropathological changes, such as hypertrophy of the cerebral cortex and volume loss in the forebrain of the hypothalamus, as direct consequences of treatment with typical and newer neuroleptics, in rodents, cats, nonhuman primates, and humans (e.g., Frazier et al., 1996; Gur et al., 1998; Halliday et al., 1999; Lohr, Caligiuri, Manley, & Browning, 2000; Selemon, Lidow, & Goldman-Rakic, 1999). This work only adds to the overwhelming experimental and clinical evidence implicating neuroleptics as direct causes of tardive dyskinesia, a movement disorder which usually persists indefinitely even after drugs are withdrawn.

In the current zeitgeist, if a *single* such anatomical anomaly could be irrefutably attributed to "schizophrenia," it would launch a new research program into the "neuropathology of schizophrenia," generate endless speculation about its impact on patients' functional impairments, and be reported on the front pages and covers of the nation's newspapers and magazines. However, when pathological brain changes are observed in connection with neuroleptic drug treatment, they qualify at best as a footnote. If extremely subtle, as yet impossible-to-detect neuropathology is said to cause schizophrenia, then should we not entertain the hypothesis that not-so-subtle, detectable drug-induced neuropathology could cause worse than schizophrenia?

Discussion

This review has identified several failings of research on the drug treatment of schizophrenia. The gist of the argument constructed in the preceding pages is the following: substantial evidence exists to suggest that the quality of research on the psychop-

harmacological treatment of schizophrenia has been uniformly poor, or is conducted in such a way as to make results of drug trials and other studies appear in the best light possible for the tested drugs, or studiously ignores important research directions that might highlight negative effects of drug treatment. That experienced researchers fail to control for important sources of bias and fail to describe them clearly in their reports, that journal editors and scientific forums publish papers with such obvious confounds without requiring authors to clearly note them or without establishing stricter guidelines for what will count as "evidence" to establish claims of effectiveness, are heavy blows to the scientific quality of the evidentiary basis for neuroleptic drug treatment. Speaking only of publication bias (the tendency whereby favorable results are published more frequently and more rapidly), Chalmers (1990) argues that "failure to publish an adequate account" of a clinical trial "is a form of scientific misconduct that can lead those caring for patients to make inappropriate treatment decisions" (p. 1405).

Two related issues can only be mentioned briefly here. First, this review is not exhaustive. Several important methodological points that might highlight further deficiencies have been omitted, including how subjects in clinical trials are recruited, what criteria are applied to qualify them for participation in a drug trial, whether all drugs they ingest are reported, how therapeutic and adverse effects are detected and rated, and how pharmaceutical company representatives and research site staff interact (e.g., Mason, Bermanzohn, & Siris, 1998). Second, similar conclusions have been reached by investigators about antidepressants (Antonuccio, Danton, DeNelsky, Greenberg, & Gordon, 1999; Fisher & Greenberg, 1997; Moncrieff, 2001) and stimulants prescribed for the treatment of ADHD (Agency for Health Care Policy and Research, 1999; Breggin, 2000; Schachter, Pham, King, Langford, & Moher, 2001). Reviewers find major methodological shortcomings and question the clinical applicability of findings from RCTs, faulting these studies for their ultrashort durations, lack of robustness of findings, large dropout rates, large number and heterogeneity of outcome results used, indications of publication bias, etc. The most recent analysis of a technique contrived to produce positive results for drug treatments appears as the finishing touches were put to the present article. Zimmerman, Mattia, and Posternak (2002) analyzed 31 antidepressant trials published from 1994 to 1998 in five leading psychiatric journals. They found that between 60% and 85% of patients diagnosed with major depression and who are most likely to be prescribed antidepressants in a typical outpatient psychiatric practice would be excluded from a clinical trial for a new antidepressant drug, because of co-morbid conditions or a symptom severity score falling below the cutoff point required in the 31 trials. From the trial sponsors' viewpoint, including these representative patients in a clinical trial might reveal that they do not respond to the tested drug. Zimmerman and colleagues caution: "If antidepressants are ineffective [for some of these large subgroups of depressed patients], their prescription incurs an unjustifiable exposure of risks and side effects" (p. 471).

Implications for Social Work Education

If the analysis presented here has any validity, professionals and scholars interested in the treatment of schizophrenia and mental disorders and psychological distress in general must look afresh at the ideological, ethical, political, and commercial incentives that drive the field today. Science, and pseudoscience, do not take place in a vacuum. Given its ubiquitousness as a mental health intervention, psychopharmacology cannot be studied in isolation from the internal dynamics and external constraints on the professions which assist it, practice it, or long to practice it. The critique of schizophrenia drug treatment studies presented in this article suggests that published reports simply cannot be taken at face value and summarized without pointed critical analysis, as is customary in the few social work articles on one or another psychotropic drug class. A social work student or educator guided by an "evidence-based" approach when confronting the mass of psychopharmacological studies might understandably take refuge in the large number of trials reporting positive outcomes and might conclude that antipsychotics are the best available option for the majority of schizophrenic patients, or that their beneficial effects outweigh their adverse effects. Though well-accepted at present, such conclusions would be quite imprudent.

A critical analysis must attempt to step outside of the dominant reasonings and representations surrounding a particular object of study. More to the point, such an analysis must include these particular reasonings and representations as part of the object of study. However, stepping out of dominant discourses is not easy to do because the researcher and the clinician may be enveloped in them to the point of not recognizing them. One approach particularly relevant for social work, a value-steeped profession, is to construct an analysis from first principles: values. This may reveal important inconsistencies between discourse and practice. Another approach is to analyze an object in terms of its power relations (e.g., Abraham, 1995; Cohen & McCubbin, 1990; Keen, 1998). "Findings" from psychopharmacotherapy studies must be *contextualized* in order to make sense. They must be placed squarely in their historical, ideological, economic, and political (read "power") contexts. Here are just a few elements of each context, specifically emphasizing issues that this author has rarely seen discussed in the social work literature.

History. Several works have presented compelling arguments that the treatments imposed on individuals diagnosed with schizophrenia have not improved their condition but have actually worsened it (see, most recently, Gelman, 1999; Gosden, 2001; Whitaker, 2001). By ignoring patients' own accounts and perspectives of their treatments, by neglecting the life that patients lead outside the institution and after treatment, and by excluding crucial data that they had themselves gathered, investigators and clinicians throughout this century declared one brain-disabling treatment after another a "major therapeutic breakthrough." Insulin coma, metrazol coma, electroconvulsive therapy, as well as frontal lobotomy were each promoted in their time as major "innovations." Of note, their perceived effectiveness was not estab-

lished by demonstrating that patients got well, but by flooding psychiatric journals, professional conferences, and the popular press with carefully crafted reports.

It would be regrettable if social work educators glossed over these past episodes as mere historical curiosities. On the contrary, the present system of care for seriously disordered individuals is a direct outgrowth of our previous pains. One may argue that nothing but the failures of successive new treatments (e.g., the psychopathology hospitals in the 1920s, or the convulsive and psychosurgical treatments of the 1940s and 1950s, or the drug treatments of the 1960s and 1970s, or the "community treatments" [read "drug treatments in the community"] of the 1980s and 1990s) set the stage for widespread disillusionment with each contemporary approach and for enthusiastic welcome of the next promising treatment.

In a unique meta-analysis of 368 schizophrenia outcome studies spanning one hundred years (1895-1992), Hegarty and colleagues (1994) showed that improvement rates of neuroleptic treatment and convulsive treatments were quite similar: 46% and 42%, respectively. Particularly relevant to our discussion is the observation that improvement in schizophrenia declined after the 1970s, reaching the rate of 36% in the 20 neuroleptic outcome studies published since 1986, "a level that is statistically indistinguishable from that found in the first half of the century" (p. 1412). Obviously, schizophrenia treatment has changed, and the mental health system has changed over the century, but these humbling figures—the historical perspective—attest that nearly 50 years of widespread drug therapy have *not* translated into genuine progress, as measured, for example, by a small but steady increase in recovery rates for schizophrenia.

Ideology. As discussed, the much-publicized introduction of "new, improved" drugs creates the impression that there is unequivocal *progress* in treating psychosis. This in turn reinforces the dominant idea that schizophrenia represents a genetically predisposed, environmentally triggered, neurodevelopmental brain disease which, at this state of our knowledge, best responds to chemical intervention. The idea that the distress and disorders we refer to as mental illness are genuine physical diseases completely pervades our culture. The idea that nearly one third of adults and nearly one fifth of children (the proportion of people currently diagnosable with DSM disorders) suffer from "biochemical imbalances" is taken for granted—not to say celebrated—by leaders of science and opinion. This notion is usually presented as self-evident scientific progress over earlier conceptions of an invisible unconscious ruling human behavior. However, social workers need to grapple with the implications of this notion, as it ultimately relates to empowerment of individuals and families. Specifically, they must ask whether in the not-too-distant future, we will look back on both the "unconscious conflict" and "biochemical imbalance" slogans and realize that neither had genuine scientific backing yet both were accepted and promoted uncritically by mental health experts, both were used to explain any form of psychological distress, but both ultimately left people more helpless because their message was "the problem is inside you but out of your control."

Because it is chronic, because it resembles organic forms of psychosis, because its symptoms are difficult to comprehend psychosocially, and because its experience can generate immense suffering to individuals and their families, schizophrenia has long been conceived as a progressive brain disease and is often compared to neurodegenerative diseases such as Alzheimer's or multiple sclerosis. Yet, as Siebert (1999) argues, no known brain disease has such a substantial spontaneous recovery rate: nearly one quarter of patients in the dozen long-term (more than 10–15 years) follow-up studies show full recovery, and virtually 50% show substantial social improvement. In their meta-analysis, Hegarty et al. (1994) also find a 22.5% improvement rate for "non-specific" treatments over the century (including hydrotherapy, non-neurological surgery, fever therapy, psychotherapy, placebos). It is difficult to find a social work textbook on mental health issues that stresses this crucial point or tries to build on its significance. In any case, this latter proportion represents the baseline improvement or *recovery* rate that any specific intervention must substantially exceed in order to qualify as a major improvement in the care of long-term psychosis. If the centuries-long history of psychopharmacology serves as a guide, it takes more than a few years to establish whether a new treatment was really a breakthrough. More important for consumers, it takes more than a few years to discern how many thousands of individuals have been left damaged in its wake. Until longer-term data are in, atypical drugs should be appraised with the large dose of scientific skepticism warranted by the uninterrupted history of past failures.

Politics and Economics. The overwhelming influence of the pharmaceutical industry on scientific, clinical, and regulatory independence and integrity in medicine is now recognized well beyond the few critics who have alerted us to this influence (e.g., in the mental health field, see Breggin, 1991; Ross & Pam, 1995; Valenstein, 1998). Unceasingly, investigative reports and academic studies expose a vast web of conflicts of interests pushing medical journal editors to ever-stringent yet seemingly ineffective defensive measures. Recently, studies have revealed that most authors of clinical practice guidelines have financial ties to companies manufacturing drugs recommended in the guidelines (Choudhry, Stelfox, & Detsky, 2002); that a substantial portion of pharmacotherapy articles are ghost-written by drug company or communication agency employees such that listed authors may never have seen the raw data, let alone collected it (Boseley, 2002); that negative results from clinical drug trials are sent "to the nether regions," (Vergano, 2001); that multiple versions of a single study are published under different authorship such that claims for efficacy appear well-supported (documented in the case of the newer antipsychotic risperidone by Huston & Moher, 1996); etc. Commenting on a small subset of these practices, Healy (2002), himself a prolific psychopharmacology author and researcher, states that it is unclear how much of the body of drug treatment studies published in mainstream psychiatric journals may be legitimately considered "scientific literature." Healy asks: "Is this field scientific anymore? If science involves the pursuit of anomalies or efforts to refute received wisdom, then it is

hard to characterize the field as scientific." This judgment is echoed in the present article.

In addition, it has become clearer how pharmaceutical companies use public relations techniques, including aggressive funding of front groups or "partners," to advocate for the availability of new psychotropic drugs (Gosden & Beder, 2001). For example, the most influential and widely respected nonprofit lobby group in mental health, the National Alliance for the Mentally Ill (NAMI), which "fought long and hard on moral grounds alone for making the new atypical antipsychotics and [selective serotonin reuptake inhibitors] more widely available" (Bentley & Walsh, 2001, p. 239), received, according to Silverstein (1999), nearly $12 million from 18 drug firms between 1996 and mid-1999. All other considerations aside, atypical antipsychotics are very big business: in 2001, the market for a single such drug, Eli Lilly's Zyprexa (olanzapine), surpassed $2.5 billion, almost equivalent to the bestselling Prozac (Hensley & Burton, 2001).

The issue today is no longer whether these conflicts of interest have diluted and sullied the scientific imperative in medical research, but how much they have done so, and what to do about it. These conflicts of interest flourish because of the immense power of the pharmaceutical industry in the modern health care system, a power sustained by an interlocking system of privileges and benefits, tax cuts and subsidies, bestowed by governments. Targeting one well-paid lobbyist toward every single member of Congress, the pharmaceutical industry uses every means of persuasion and advertising at its disposal to continue to enjoy its status as the most profitable industry in the world and to shape science, clinical practice (of medical and nonmedical health professions), public opinion, and regulation in its favor (Public Citizen, 2001). Even the Food and Drug Administration, charged with approving new drugs to market and overseeing the safety of pharmaceuticals once they are marketed, depends on the pharmaceutical industry to pay the salaries of 10% of its workers and to equip itself with new computers (Timmerman, 2002).

Can Social Workers Reconstruct Psychotropic Drugs?

Cohen, McCubbin, Collin, and Perodeau (2001) have commented that generally,

> social researchers interested in medications have implicitly treated them in a way quite consistent with the technocratic discourse—as technological products to be consumed in satisfaction of precisely identified needs—and with its companion biomedical discourse—as tools of practitioners who possess specialized knowledge to determine their appropriate use. (p. 442)

These authors argue that this approach has not yielded the insights necessary to make sense of the numerous rationalities and irrationalities of (psychotropic and other) medication use. Yet the technicist approach appears to be implied in various texts by social work authors. For example, in an introductory article on psychopharmacology and social work practice, Dziegielewski (1998) expresses her aim as "establishing a basis for understanding medication use" (p. 371), but

her discussion focuses on technicalities such as basic medication terminology and rules of medication use. To be sure, it is a competent discussion, but it suggests to the present author that more imaginative and critical treatments are necessary to "provide basic information for the health care social worker as well as a foundation to encourage the social worker to seek and learn more" (p. 382).

In their detailed book on social workers and psychiatric drugs, Bentley and Walsh (2001) describe the educator role—one of several roles available to social workers—as consisting of "helping clients and their families understand the reasons for medications and other treatments, the benefits and risks of such treatments, and the various treatment options available to them" (p. 276). If anything, this article has suggested that fulfilling such a role requires more than keeping abreast of the latest literature—it requires independent, critical assessment of the relevant literature (e.g., as Kirk & Kutchins, 1992, have done for the DSM and Gomory, 1999, has done for programs of assertive community treatment). It is ventured that most social workers do not seem currently equipped, nor might they be interested, to undertake such a demanding duty. Perhaps this is a consequence of social workers being professionals trained to focus on concrete tasks. Thus, monitoring for side effects, reporting compliance problems, preventing medication errors, providing answers about basic client questions, may, by definition, restrict psychopharmacological content in social work education to technical and descriptive issues surrounding the day-to-day ingestion of drugs by individual clients. Specialist social work authors might thus end up merely summarizing, in accessible language for busy practitioners, the mass of available "information" existing in the psychopharmacological fields.

Can there be a unique voice of social work about psychotropic drug treatments? Can social workers actually use their own conceptual or practice models to create order out of psychopharmacological chaos? Difficult questions, to be sure. However, it is here proposed that if social workers want their knowledge of psychotropic drugs to be taken seriously, then they should consciously develop their own critical appraisals of these drugs, their development, their uses and misuses by the numerous actors involved in the life cycle of drugs, and the scientific, historical, ideological, cultural, and political matrices which determine who uses (and prescribes) which drugs and why.

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