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Neuroleptic Drug Treatment of Schizophrenia: The State of the Confusion

David Cohen

Université de Montréal

This article contends that the enterprise of neuroleptic drug treatment of schizophrenia is conceptually and clinically — though not economically — bankrupt. Although new drugs spur hope and reinforce the dominant treatment paradigm, evidence from reports published during the last five years in leading psychiatric journals suggests that psychopharmacologists do not know what are the optimal doses of the most widely-used neuroleptics; that most patients do not "respond" to neuroleptic treatment; that toxic effects are routinely misdiagnosed; that prescribing guidelines may have no impact on actual prescription patterns; that claims that the popular "atypical" neuroleptic clozapine is free of extrapyramidal symptoms are completely false; and finally, that penetration of the double-blind in studies of the effectiveness of psychotropics over placebos may be a common occurrence. In the light of these findings, it is argued that the field is in crisis and that major, paradigmatic change is absolutely necessary.

The major change this century in the psychiatric treatment of the various conditions labelled "schizophrenia" or "the schizophrenias" has come from the introduction of chlorpromazine and other phenothiazines in the early 1950s. This was followed by similar drugs variously called major tranquilizers, antipsychotics or neuroleptics. For nearly 40 years, apart from the studies and reviews of a very small group of researchers, including psychiatric critics (e.g., Breggin, 1983, 1991; Ciompi, Dauwalder, Maier, Aebi, Trütsch et al., 1992; Cohen, 1988; Fischer and Greenberg, 1989; Karon, 1989; Kiesler and Sibulkin, 1987; Mosher and Menn, 1978; Paul and Lentz, 1977; Warner, 1985), there has been near-universal consensus in the scientific literature, as well as in popular media reports, that neuroleptics have been the most useful treatment for schizophrenic psychoses, unsurpassed by any other form of

Requests for reprints should be sent to David Cohen, Ph.D., Director, Groupe de recherche sur les aspects sociaux de la prévention (GRASP), Université de Montréal, C.P. 6128, succ. Centre-ville, Montréal, QC, Canada H3C 3J7.

intervention. This attitude is well reflected in the opening sentences of a recent research report, which reads: "The antipsychotic efficacy of neuroleptics has been confirmed in numerous studies based on a meticulous method . . . . It is only antipsychotic medication that enables many patients to benefit from [other interventions]" (Windgassen, 1992, p. 405, references deleted).

This consensus showed, from the early 1980s onward, some signs of strain. The behavioral toxicity and numerous iatrogenic effects of neuroleptics (especially the late-appearing involuntary movement disorders) came to be increasingly recognized, or, more to the point, increasingly discussed by leading psychiatric researchers and the American Psychiatric Association (e.g., APA, 1985, 1992; Task Force, 1980; Van Putten and Marder, 1987). In 1986, even Pierre Deniker (credited, with Jean Delay, of having introduced chlorpromazine in psychiatry), published an article entitled "Are the Antipsychotic Drugs to be Withdrawn?" (Deniker answered his question in the negative.)

However, these minor doubts appear to have given way, in the early 1990s, to a wave of renewed optimism (at least in North America) about the drug treatment of schizophrenia, one based partly on the introduction of new or formerly shelved antipsychotics such as risperidone and clozapine. These compounds, loosely referred to as "atypical" neuroleptics because their dopamine receptor binding differs from that of most drugs currently in use, are stated to be equal to or superior than the older neuroleptics, especially for "treatment-resistant" or "neuroleptic non-responsive" patients, and to produce vastly fewer side effects. For example, the advertisement for risperidone in the April 1994 issue of the *American Journal of Psychiatry* states that "incidence and severity of extrapyramidal symptoms (EPS) were similar to placebo."[1] These newer drugs create, in the minds of many users, such as patients, families, governmental bodies, and the media, the impression that although there continue to be many hurdles to understanding and treating schizophrenia, there is nevertheless *progress*. This in turn reinforces the dominant paradigm in North America that "schizophrenia" represents some sort of genetically predisposed, environmentally triggered, neurodevelopmental brain disease which, at this state of our knowledge, best responds to chemical intervention.[2]

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[1]According to Kerwin (1994), all risperidone trials involved a short washout period of one week. By itself, this may easily explain unusual findings such as extrapyramidal effects in the "placebo" group. That such a predictable confound is ignored and results elevated to the status of a major improvement in schizophrenia treatment shows the desperation in the drug treatment field (see below).

[2]For different views on the nature of "schizophrenia," see Boyle (1990), Sarbin (1990), and Wiener (1991), among others. Stoll, Tohen, Baldessarini, Goodwin, Stein et al. (1993) reported

Nevertheless, the position advanced in this paper is that the neuroleptic drug treatment of schizophrenia is today, quite simply, in a mess. This thesis will be supported by a selective review of research reports published during the last five years in leading psychiatric and medical journals, reports touching on basic aspects of use, prescription, and evaluation of neuroleptic and other prescribed psychiatric drugs. This review leads to the suggestion that the enterprise of drug treatment of schizophrenia is conceptually and clinically — though certainly not economically — bankrupt, and calls for major paradigmatic change. That such change is urged only by critics of psychiatry or by researchers in other disciplines reinforces Kuhn's (1970) oft-cited thesis about the powerful inertia of scientific systems; or Karon's (1989, p. 146) conclusion (following an in-depth review of medication versus psychotherapy studies) that "political and economic factors and a concentration on short-term cost-effectiveness, rather than the scientific findings, currently seem to dictate [drug treatment of schizophrenia]"; or Cohen and McCubbin's (1990) observation that systematic power imbalances between interested parties in the drug prescription situation ensure that only "scientific findings" favouring the interests of the most powerful parties will be legitimated as such.

This paper discusses the results and implications of a small number of published reports of investigations about neuroleptics and other psychotropics conducted by different researchers. No attempt is made to uncover and review all the literature bearing on the topic, and no claim is made that the findings from these studies are representative of findings of most studies on drug treatment. However, it will become clear that evidence to corroborate the main thesis is widely available. In all probability, such evidence will continue to accumulate, along with recognition that the leading treatment approach is not only inadequate, but is the source of the problems here discussed.

The State of the Confusion

What Dose Should We Use?

The basic factor involved in the prescription of any drug for the treatment of any undesirable condition is determining appropriate dose. After nearly 40 years of intensive psychopharmacological research and clinical experience with neuroleptics on hundreds of millions of patients throughout the world, one would expect the dosage of neuroleptic drug administration to be well-mapped. In particular, considering that neuroleptic use is associated with seri-

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a 300% decrease in the frequency of schizophrenia diagnoses (in parallel with a 400% increase in the frequency of diagnoses of major affective disorders) in six North American psychiatric teaching hospitals from 1972 to 1988. These results highlight the absurdity of viewing these conditions as genetically provoked brain diseases.

ous toxic effects, many of which appear to be dose-dependent, one would also expect the minimum effective dosage of various neuroleptic agents to be known. This, however, is not exactly the case. The phrase "minimum effective dosage" is important, since it is specifically what the official APA prescribing guidelines urge clinicians to utilize in chronic treatment (APA, 1992, p. 251).

In a study by Rifkin, Doddi, Karajgi, Borenstein, and Wachspress (1991), 87 newly admitted inpatients with a diagnosis of schizophrenia were randomly assigned to three neuroleptic-treatment conditions: one group received 10 mg/day of haloperidol, one group received 30 mg/day, and a third group received 80 mg/day. Subjects were then evaluated (using state-of-the-art symptom scales) under double-blind conditions for six weeks. At the end of this period, no differences in clinical condition were noted between the three groups.

To understand the significance of this finding, one must remember that haloperidol has been in use for about 30 years and is considered the "gold standard" treatment for schizophrenia ("Major advance," 1993). It was estimated to be the second most-frequently prescribed neuroleptic in the United States in 1985 (Wysowsky and Baum, 1989). Its effects on animals and humans are extremely well documented. Furthermore, the difference between 10 mg and 80 mg of haloperidol is very great, roughly equivalent to the difference between 500 mg and 4000 mg of chlorpromazine (at the time of the study, 20–25 mg/day of haloperidol was considered a "standard dose"). Still, what these results suggest is that, after all this time and clinical experience with haloperidol, we still cannot predict different effects of gross dosage variations of this drug, nor do we know what is its optimal dose (for the treatment of acute "schizophrenia").

Is this ignorance limited to haloperidol, or are we in the dark about other drugs? One answer is given by Kane (1989), who notes that it is still not possible to relate blood level of a neuroleptic to observed clinical response and that "questions remain as to what specific drug should be used [and] what dosage for what duration is needed . . . " (p. 323). Another, more diplomatic answer is found in a report by Waddington, Weller, Crow, and Hirsch (1992), summarizing the presentations at a recent international conference on schizophrenia: ". . . there is renewed appreciation of our previous failure to establish, even at this late stage in their evolution, the optimal usage of *existing typical neuroleptic drugs* and of the potential benefit still to be gained therefrom" (p. 994, emphasis added). Bitter, Volavka, and Scheurer (1991), for their part, are more direct: "Despite intensive research and after almost four decades of neuroleptic treatment we still do not know the minimum effective dose of any neuroleptic" (p. 32).

What is the Rate of Nonresponse to Neuroleptic Treatment?

Since the recent introduction (in North America) of clozapine, a drug marketed specifically for "neuroleptic nonresponders," we have been hearing very much about this group of schizophrenic patients. Previous discussions of this particular difficulty with neuroleptic treatment were rare, and one would get the impression from the literature that almost no one did not "respond" to such treatment, especially since it is administered to the overwhelming majority of people diagnosed as schizophrenic. Recently, though, some reports estimated a 5–25% nonresponse rate (e.g., Brenner, Dencker, Goldstein, Hubbard, Keegan et al., 1990). Informed observers have suspected that the rate is much higher (e.g., Easton and Link, 1986-87).

The most typical standard to evaluate the *effectiveness* of neuroleptic treatment of schizophrenics has been that of relapse (usually defined as rehospitalization for an acute psychotic episode, or a marked increase in symptoms as measured by instruments such as the *Brief Psychiatric Rating Scale*). Generally, two groups of comparable patients, one administered neuroleptics and the other a placebo, are followed for a determined period (usually 4 to 12 months, occasionally 24 months) after release from an index hospitalization. Effectiveness is measured by comparing the number of patients who relapse in each group. Hundreds of neuroleptic effectiveness studies have been carried out since the late 1950s, and the overall rate of effectiveness reported is very similar to the rate recently estimated by Davis, Kane, Marder, Brauzer, Gierl et al. (1993) from 35 random-assignment, double-blind studies involving 3720 patients: "patients on placebo relapse at a rate of 55%, whereas only 21% of schizophrenic patients relapse when they are on maintenance therapy" (p. 24). Subtracting from the placebo rate the 21% of patients *who would have relapsed even if they were on drugs*, we obtain the net effectiveness rate of 34%, or one in three schizophrenic patients for whom neuroleptics appear to delay relapse during a set study period.

To properly evaluate the effectiveness of neuroleptics in schizophrenia, however, one should consider, in addition to relapse, key outcome measures like social integration and employment, that are now taken into account in most long-term outcome studies. Yet, according to Meltzer (1992), "*there are no studies* that demonstrate the outcome of neuroleptic treatment in schizophrenia using all these criteria" (p. 516, emphasis added).

The results of an unusual investigation by Keck, Cohen, Baldessarini, and McElroy (1989) raise other disturbing questions concerning the effectiveness of neuroleptics. These authors reviewed relevant studies in order to define the onset and time course of antipsychotic effects of neuroleptic drugs. They excluded open trials, studies of chronically psychotic patients, and studies not using a placebo or non-neuroleptic sedative as a control, which left only

five reports out of more than 1,300 published studies on the efficacy of neuroleptics. In the three studies of neuroleptic vs. placebo, and the two of neuroleptic vs. sedative, "[T]he same overall degree of improvement was observed during treatment . . . within each of the markedly different time intervals studied. Furthermore, when a neuroleptic was compared to a sedative — diazepam or opium powder — the sedative demonstrated efficacy similar to that of the neuroleptic during the first day and through 4 weeks of treatment" (pp. 1290–1291, references deleted). In a letter to the editor commenting on these results, an admittedly baffled psychiatrist wondered: "Has our clinical judgment about the efficacy of antipsychotics been a fixed, encapsulated, delusional perception . . . ? If there is no difference in outcome in a month, how about 2 months, or 6, or a year, or a lifetime? Do sedatives prevent relapse as well as antipsychotics do? Are we back to square 1 in antipsychotic psychopharmacology?" (Turns, 1990, p. 1576).

We may now return to the question posed at the start of this section: What is the rate of "nonresponse" to neuroleptic treatment for acute episodes of schizophrenia? One answer is found in the results of a study conducted by Johns, Mayerhoff, Lieberman, and Kane (1990), which was published as a chapter in a book entitled *The Neuroleptic Nonresponsive Patient.* In this study, researchers first administered a standard dose of a high-potency neuroleptic (20 mg/day of fluphenazine) to 29 "acutely exacerbated, hospitalized chronic schizophrenic patients," and obtained a response rate of 37%. Although this seemed "surprisingly low" to the authors, review of an earlier pilot study undertaken with 31 similar patients "revealed an almost identical response rate (35%) to the same treatment condition" (p. 62). The authors found that "Only one-third of such patients responded well to an initial 4-week course of neuroleptic treatment; continued neuroleptic treatment for an additional 4 weeks regardless of whether the neuroleptic class or dose was changed or held steady, resulted in almost no further improvement in clinical condition" (p. 63). Additional data from this ongoing study has been published, with the sample size increased to 156 "acutely ill schizophrenic, schizoaffective, and schizophreniform" hospitalized patients (Kinon, Kane, Johns, Perovich, Ismi et al., 1993). Of the 115 patients who completed the first four-week phase of the study, 68% were rated as non-responders. Of the nonresponders who went on to randomized treatment (lower dose, higher dose, or other neuroleptic), "only 4 of 47 subjects (9%) subsequently responded" (p. 309). Despite their earlier surprise, the authors now characterize the 68% nonresponse rate as "consistent with a range in previous reports" (p. 310).

Because of the scarcity of systematic studies focusing on nonresponse, it is difficult to assess how common this response is in typical practice. However, Collins, Hogan, and Awad (1992) rated 50% of all schizophrenic patients

hospitalized for more than six months in Ontario's largest psychiatric hospital as nonresponders (although these patients were maintained on daily neuroleptic doses as high as acute patients!). Further, Meltzer's (1992) comprehensive review of treatment strategies for neuroleptic nonresponders begins by estimating, matter-of-factly, that up to 45% of patients do not respond to neuroleptics or develop such severe drug-induced behavioral toxicity that treatment cannot be continued.

Can We Tell a Side Effect When We See One?

The issue of side effects[3] resulting from neuroleptic treatment is certainly the most daunting problem in this field today. It has received an enormous amount of attention during the last few years, including books with such titles as *Adverse Effects of Psychotropic Drugs* (Kane and Lieberman, 1992), or the more evocative *Drug-Induced Dysfunction in Psychiatry* (Keshavan and Kennedy, 1992), or *Toxic Psychiatry* (Breggin, 1991).

Most patients receiving neuroleptic drugs will experience one or another of a multitude of undesirable effects, ranging from sedation, dry mouth, loss of sexual desire, to various acute or tardive movement disorders known as extrapyramidal symptoms (EPS); these include parkinsonism, dystonia, akathisia, and tardive dyskinesia. According to the manufacturers of risperidone, EPS "are observed in 75 to 90% of patients on neuroleptic therapy and are the major cause of noncompliance and relapse" ("Effect of risperidone", 1993, p. 1).[4] In their tardive forms, EPS rarely respond to any treatment and are usually irreversible (Gualtieri, 1993). The situation is further complicated by the fact that some of the most common manifestations of acute EPS, such as akinetic depression or akathisic agitation, are indistinguishable from, respectively, psychotic withdrawal or agitation, considered to be core symptoms of schizophrenia (Rifkin, 1987; Van Putten and Marder, 1987).

It is thus important to know how clinicians detect the presence of neuroleptic-induced behavioral toxicity. To this author's knowledge, the only pub-

[3]It is beyond the scope of this paper to discuss the inappropriateness of the term "side effect." Although we find in the psychopharmacological literature a clear distinction between "primary" and "secondary," or "main" and "side" effects, there are few discussions of what a "side" effect *is*. What distinguishes the two types of effects appears to be simply the *intent* of the prescriber and has nothing to do with the pharmacological action of the drug, nor does it rest on any "objective" consideration such as frequency, intensity, or duration of the effect.

[4]It is unusual to see such high estimates of EPS and such frank statements to the effect that EPS cause relapse, especially from a pharmaceutical company. However, risperidone is marketed on the basis of its low propensity to produce EPS: statements that other neuroleptics produce a high rate of EPS thus reflect favorably on the new drug. This tendency, to frankly and publicly acknowledge the ill-effects of widely used treatments only when a *new* treatment arrives on the scene, characterizes the introduction of most somatic treatments in psychiatry (insulin coma, ECT, lobotomy, neuroleptics, and now, "atypical" neuroleptics).

lished study to have specifically addressed this issue was conducted by Weiden, Mann, Haas, Mattson, and Frances (1987). The investigators compared well-trained clinicians' recognition of the major EPS in 48 psychotic inpatients with independent blind diagnoses by researchers using standardized rating scales. For all types of EPS, there were striking rates of disagreement between the research and the clinical diagnoses. Only one of ten patients with tardive dyskinesia, seven of 27 patients with akathisia, and 17 of 26 patients with parkinsonism were accurately diagnosed by the clinicians. Furthermore, every single case of acute EPS that was recognized by clinicians was initially treated by adding another drug, an antiparkinsonian. Not once did clinicians reduce the neuroleptic dose, which had caused the EPS in the first place. Without significant changes in diagnostic and medical training, the authors conclude, "it is likely that extrapyramidal side effects will continue to be underdiagnosed at an alarmingly high rate" (p. 1153). In a later study, it was suggested that a four-hour course in diagnosis and management of EPS resulted in better recognition of EPS and lower neuroleptic doses prescribed by psychiatric residents (Dixon, Weiden, Frances, and Rapkin, 1989). Reviewing the curricula of five local psychiatric residency programs, the investigators found that "a mean of only 0.5 hours" (p. 104) is spent specifically on EPS.

Are We Getting Better at Prescribing Neuroleptics?

In a rare follow-up study of prescription patterns conducted on a sizeable group (N= 253) of chronic psychiatric patients, Segal, Cohen, and Marder (1992) compared psychotropic drug prescriptions in the sample in 1973 and 1985. The initial impetus of the study was to document how, in light of published reports, professional guidelines, adverse publicity about the dangers of EPS and an increasing amount of tardive dyskinesia (TD)-related litigation, psychiatrists had (probably) modified their prescribing habits, in conformity with the 1980s consensus about neuroleptic use. This consensus included, among other recommendations, lowering doses for patients on long-term treatment. The findings: over the 12-year period, daily doses *doubled*, from about 500 mg/day in chlorpromazine-equivalent in 1973, to about 1000 mg/day in 1985 (almost identical results are reported by Reardon, Rifkin, Schwartz, Myerson, and Siris [1989], in a multi-center longitudinal study, from 1973 to 1982).

More unexpectedly, patients prescribed their drugs by psychiatrists, versus those prescribed drugs by nonpsychiatric physicians, were receiving the highest doses at follow-up (even when other variables — such as number of hospitalizations, psychiatric symptoms, place of residence, etc. — were held constant). Thus, nonpsychiatric physicians, less trained in the use of neuro-

leptics and less sensitized to their adverse effects, were more prudent in their prescribing than psychiatrists. In addition to using lower doses, nonpsychiatrists prescribed less potent neuroleptics and fewer concomitant drugs.

There are numerous indications in the recent literature that "low" doses of neuroleptics, in the range of 3–5mg/day of oral haloperidol (the so-called threshold dose[5]) may be effective for about 70% of acutely psychotic schizophrenic patients within five weeks (e.g., Hogarty, 1993). It remains to be seen how — and when — such findings will be applied in everyday clinical settings. There is, however, no reason to be optimistic. Segal et al. (1992) suggest that prescribers respond to varied imperatives when deciding how to prescribe drugs. Lacking tools other than psychotropic drugs to prevent schizophrenic relapses, they are reticent to err on the side of caution by prescribing less. Cohen and McCubbin (1990) suggest that information on drugs or side effects *cannot*, by itself, lead to a change in psychiatric prescription patterns — the field is simply not governed by scientific considerations, nor are the ultimate consumers, the patients, in any position to effect change.

Are We Responsible Enough to Use Neuroleptics?

Clozapine is said to be an "atypical" antipsychotic because it appears to bind selectively to different dopamine receptors than the vast majority of neuroleptics routinely available in North America. This substance, used modestly in Europe since the early 1960s, had its use greatly restricted after a series of about 20 deaths due to agranulocytosis (sharp drop in white blood cells) in 1975 in Finland and Switzerland (Kerwin, 1994). The other major drawback of clozapine is a tendency to cause convulsions, in a dose-related manner. In 1990, Sandoz reintroduced clozapine in Canada and the United States, with great media fanfare (including a *Time* magazine cover story published on July 6, 1992), as a treatment effective for the (suddenly) numerous category of nonresponsive and treatment-resistant patients (estimated at 30% in the *Time* article). Healy (1993) notes that "With the problems of launching clozapine in the US and the UK owing to its toxicity, company-sponsored research has focused on a treatment-resistance indication," although previous studies from Europe showed that the drug's efficacy for schizophrenia "has been no more and no less than that of other neuroleptic agents" (p. 25).

As an added, incredible bonus, clozapine was depicted in practically every publication, and every advertisement by Sandoz, to be remarkably free of

[5]According to the neuroleptic threshold theory, the "threshold dose" (or minimum effective antipsychotic dose of a neuroleptic) correlates with the appearance of "fine motor" symptoms (micrography) as opposed to the appearance of manifest or "coarse motor" EPS (see Bitter et al., 1991; McEvoy, 1986).

EPS.[6] For example, the advertisement for clozapine in the January 1990 issue of the *American Journal of Psychiatry* contains the following headline: "Hope continues with a virtual absence of certain acute extrapyramidal symptoms." Some researchers, such as Schwartz and Brotman (1992), state simply that clozapine "does not cause extrapyramidal effects" (p. 981). This affirmation was, in almost every instance, accompanied by a statement to the effect that there had not yet been any "confirmed cases" of tardive dyskinesia associated with clozapine.

A mere three years later, aside from several reports of clozapine-induced side effects typical of phenothiazine neuroleptics, such as major weight gain (Wiebe, 1993), priapism (Rosen and Hano, 1992; Seftel, Saenz de Tejada, Szetela, Cole, and Goldstein, 1992; Ziegler and Behar, 1992), and anticholinergic delirium or toxic psychosis (Szymanski, Jody, Leipzig, Masiar, and Lieberman, 1991), there is at least one published report of clozapine-associated tardive dyskinesia (DeLeon, Moral, and Camuñas, 1991; an earlier report of tardive dyskinesia exacerbation with clozapine was reported in the German literature by Doepp and Buddeberg, 1975). For their part, Nobécourt and Turgeon (1992) state that, in the few years since clozapine's introduction, "a few cases of mild tardive dyskinesia have been reported" (p. 71).

There are also several reports of the occurrence of a typical symptom of parkinsonism, hypersalivation (Bourgeois, Drexler, and Hall, 1991; Grabowski, 1992). There are also several reports of akathisia (e.g., Friedman, 1993, including one blind survey in which akathisia was observed to be similar in prevalence and severity in patients treated with clozapine and those treated with standard neuroleptics, with a worse overall clinical outcome for akathisic patients regardless of the neuroleptic used (Cohen, Keck, Satlin, and Cole, 1991). There are also reports such as the following summary of the results of a two-year prospective clozapine monitoring program carried out by W.W. Fleischhaker: "Surprisingly, some 10% of patients developed mild to moderate akathisia, and almost 40% developed tremor" (Waddington et al., 1992, p. 993). Finally, several reports have appeared about a rare but *quintessential* neuroleptic effect, the potentially fatal neuroleptic malignant syndrome (e.g., DasGupta and Young, 1991; Miller, Sharafuddin, and Kathol, 1991; Nemecek, Rastogi–Cruz, and Csernansky, 1993; Reddig, Minnema, and Tandon, 1993), although the diagnosis in some of these cases has been questioned (Weller and Korhuber, 1993).

Simply put, clozapine is not so "atypical." Still, as late as July 1993, in no less a prestigious journal than *The New England Journal of Medicine*, one

[6]The risk of agranulocytosis, however, has been well-publicized: between February 1990 and April 1991, 73 of 11,555 patients on clozapine developed this complication, and two died (Alvir, Lieberman, Safferman, Schwimmer, and Schaaf, 1993).

could read, "Unlike classic neuroleptic agents, *clozapine is not associated with the development of acute extrapyramidal symptoms* or tardive dyskinesia" (Alvir, Lieberman, Safferman, Schwimmer, and Schaaf, 1993, p. 162, italics added). Error or deception?

In a 1989 retrospective, Deniker, commenting on how his and Delay's definition of the characteristics of neuroleptics (as agents necessarily having neurological toxicity) had withstood the test of time, had this to say about clozapine:

> In 1970, Stille and Hippius announced that *clozapine* was a powerful antipsychotic without extrapyramidal effects: our theory was therefore seriously attacked. In reality, this was the exception that proves the rule. We had already experimented with clozapine, and had abandoned it on account of neurovegetative phenomena (collapse) which in the range of effects of neuroleptics are symmetrical to the extrapyramidal symptoms; but these are certainly neurological manifestations. (p. 256, italics in text)

Recently, Healy (1993) posited several reasons why the efficacy of clozapine may have been vastly over-estimated, why in fact a satisfactory double-blind study of maintenance treatment with clozapine may have been impossible to conduct. Among others, he mentions the fact that the "combination of excitement and close supervision [weekly or twice-weekly blood counts] of results can be expected to be associated with better response rates than the current neglect that is all too often visited on chronic schizophrenic patients" (p. 26). But this may be a moot point. There is no shortage of alternative antipsychotics, currently in different phases of clinical testing or regulatory approval and estimated to cost a fraction of the cost of clozapine, to take its place (Hollister, 1994). This is, of course, the case with risperidone, recently approved for clinical use in North America. During a conversation with me, a psychiatrist involved in clinical studies with the drug summed up his enthusiasm in the following words: "This drug is so amazing, patients are getting better faster than their illness allows." What seems amazing is not the power of psychoactive substances but the expectant faith and naive rhetoric of some clinicians. This pharmaceutically fueled faith, not any valid new or improved understanding of the nature of schizophrenia, is undoubtedly the driving force in the field today. This is illustrated by the title of an editorial in the *British Journal of Psychiatry*: "The New Atypical Antipsychotics: A Lack of Extrapyramidal Side-Effects and New Routes of Schizophrenia Research" (Kerwin, 1994). It is also supported by the following quote from Mitchell (1993):

> Forty years after the discovery of chlorpromazine finds us with the enthusiasm of the introduction of clozapine. At the same time, however, it is sobering to reflect on how little we have learned of the aetiology of the functional psychoses, despite the fervor generated by the excitement of the psychopharmacological discoveries of the 1950s. (p. 344)

Chlorpromazine and clozapine might have more in common than being introduced 40 years apart and generating excitement in the psychiatric profession. Other parallels come to mind: exaggerated therapeutic claims; widely-publicized personal accounts of near-miraculous recoveries; selective denial and misperception of obvious "side effects"; and relief at not having to deal fully with the public health consequences of the iatrogenic effects of previously aclaimed, equally miraculous treatments. There exists a refusal to acknowledge, let alone discuss, the immense theoretical and practical contradictions generated by the abandonment of these previous treatments. Today, Kerwin (1994) recommends that atypical antipsychotics "replace classic antipsychotics" in routine clinical practice (p. 146). The cycle continues, until another pharmaceutical innovation will lay bare the disadvantages of today's novelty.

Clozapine and its new-and-improved successors confront us with a basic question which researchers in the 1950s and 1960s had answered in the negative. Can we obtain the antipsychotic, agitation-reducing effect without producing an equivalently profound toxic effect? Can we expect the human brain to absorb drug induced disruptions in neurotransmission without compensating by symmetrical behavioral toxicity? Whatever answer we give to this key question, it is useful to remember that, to this day, selective suppression of avoidance behavior, inhibition of spontaneous locomotor activity, and the production of catalepsy in exposed laboratory rats — not merely some biochemical measure of dopamine receptor binding — still serve as the best markers of potential "antipsychotic" potency of compounds in the early phases of clinical investigation (Ahlenius, 1991).

How Do We Evaluate the Therapeutic Effectiveness of Drugs?

In clinical drug research in which the efficacy of an experimental drug is compared with a placebo substance, "blindability" is an extremely important element. It usually implies that drug and placebo are coded and dispensed in identical-appearing form so that neither the subject nor the evaluator/clinician knows which treatment is being given to whom. This is done in order to counteract the well-documented effects of subject or experimenter expectation on the evaluation of the benefits of a particular drug. Blindability takes on added importance, in the light of recent compelling reports which estimate that up 70% of patients affected with mild medical conditions respond very favorably to placebo (Goleman, 1993).

White, Kando, Park, Waternaux, and Brown (1992) retrospectively assessed the "blindability" of a clinical drug trial of etoperidone, a putative antidepressant. An evaluator was provided with all the drug trial data minus the outcome results. The evaluator was then asked to guess which subjects

had received the experimental drug and which subjects had received the placebo. The evaluator correctly guessed active drug assignment for 73% of the 22 etoperidone-treated subjects, and 67% of the placebo-treated subjects, and this on the basis of side effects alone. Distinguishing drugs from placebo on this basis was suggested in an early review by Breggin (1983, p. 59). According to more recent, comprehensive reviews (Greenberg, Bornstein, Greenberg, and Fischer, 1992; Fischer and Greenberg, 1993), side effects (including the fact that inert placebos simply do not produce the variety and intensity of physical sensations which active substances do) may be the primary reason for penetration of the double-blind. In their meta-analysis of 22 studies of antidepressant effectiveness, Greenberg et al. found that if, in addition to the new drug being tested, some patients were given an older antidepressant as a control, the new drug was only one quarter to one half as powerful as reported in studies in which the new drug was tested only against an inert placebo. In any case, according to Fischer and Greenberg (1993), there now exists "a substantial reservoir of data discrediting the integrity of the double-blind . . . [which] means that most past studies of the efficacy of psychotropic drugs are to unknown degrees scientifically untrustworthy" (pp. 345; 348). In other words, we may be justified to question seriously the validity of the very large volume of "controlled" clinical psychotropic drug research.

Conclusion

This paper has attempted to support the contention that the neuroleptic drug treatment of schizophrenia, contrary to numerous statements contained in professional and popular reports, and despite the arrival of "new and improved" antipsychotics, is at a virtual standstill and that no real progress has been made since the introduction of these drugs forty years ago. The argument is based on the following evidence.

First, psychopharmacologists do not know what are the optimal or minimally effective doses of the most widely-used neuroleptic drugs.

Second, the rate of nonresponse to neuroleptic treatment in acute and chronic schizophrenic patients is probably in the 45–70% range, not the previously stated 5–25% range. Furthermore, the net positive effect of neuroleptics, with respect to relapse prevention over a one- to two-year period, is visible only in one third of patients.

Third, even well-trained clinicians may routinely fail to recognize textbook presentations of acute EPS. When these EPS are accurately diagnosed, subsequent medication decisions may compound the problem.

Fourth, contrary to recommendations from the research literature and from official guidelines, psychiatrists who prescribed neuroleptics to chronic patients until the mid-1980s had a tendency to increase doses over time.

Fifth, despite frequent, unequivocal statements by renowned psychopharmacologists in the most prestigious psychiatric and medical journals to the effect that clozapine, a novel antipsychotic, is "remarkably free" of typical EPS, easily available evidence suggests that this is simply a false claim.

Sixth, research protocols used to determine whether a psychotropic drug is more effective than placebo may be fundamentally flawed, since the appearance of side effects has been shown to negate the blindability of clinical investigations.

Some of the above statements relate to basic knowledge about the effects of antipsychotic drugs, while others are more closely tied to how the drugs are used and promoted in everyday practice. One might argue that to mix both these aspects of neuroleptic treatment may be misleading and fail to give a true picture of this form of treatment. However, scientific studies are supposed to inform clinical practice, which, in turn, may suggest lines for scientific inquiry. What is one to make of the fact that undesirable, toxic effects of neuroleptics, unarguably more frequent and predictable than therapeutic effects, are less understood, studied, and known than therapeutic effects?

It may be also argued that, although the drug treatment of schizophrenia still "remains a quagmire for clinicians" ("Drug treatment," 1992), there are indications today that clinicians are prescribing more prudently and may be returning to the use of typical doses more reminiscent of the 1950s and 1960s. For example, recent work on the neuroleptic threshold dose has highlighted the advantages of low-dose treatment compared to standard or high doses. All this may be well and true. By the same token, however, *we have been through this before*. And it has brought us to where we are today. Lower dose treatment and a frank admission that extrapyramidal symptoms were a *sine qua non* of antipsychotic efficacy (e.g., Denber, 1959) did not really make a difference in the rational use of neuroleptics: clinicians were obviously not satisfied with the results obtained, and increased neuroleptic doses to high levels, with the results described here which any experienced clinician would recognize.[7] In conclusion, it is reasonable to entertain the suggestion that in any other field of applied scientific endeavour, results such as these would indicate that the field is in crisis, that conventional assumptions are wrong, and that major, paradigmatic change is absolutely necessary.

[7]The well-known fact that daily neuroleptic doses are, on average, much higher in the United States than in most European countries raises a host of other interesting questions about the social construction of the efficacy of treatment (see Payer, 1990).

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