From Placebo to Panacea

Putting Psychiatric Drugs to the Test

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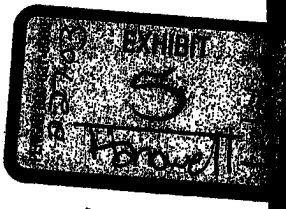

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CHAPTER 5

A Critique of the Use of Neuroleptic Drugs in Psychiatry

DAVID COHEN

OVER THE PAST 45 years, neuroleptic (NLP), or antipsychotic, drugs have been prescribed to tens of millions of individuals diagnosed as suffering from various functional and organic psychotic disorders. NLPs are the mainstay of treatment for schizophrenic patients. They are also prescribed to more than 20% of nursing home residents and individuals with developmental disabilities (Ray et al., 1993). By the mid-1980s, 19 million outpatient NLP prescriptions were written annually in the United States (Wysosky & Baum, 1989). Yet, NLPs—which include risperidone (Risperdal®), haloperidol (Haldol®), chlorpromazine (Thorazine®), thioridazine (Mellaril®), thiothixene (Navane®), clozapine (Clozaril®), and a dozen other drugs—remain among the least prescribed psychotropics.

Those who ingest NLPs rarely request them and generally dislike them very much (Wallace, 1994). The popular expressions "chemical straitjacket" and "zombie effect" well describe NLPs' unique psychomotor subduing effect, used until the mid-1980s in the former Soviet Union to disable imprisoned political dissidents. Among the different classes of psychotropics, NLPs probably produce the most substantial iatrogenic morbidity (Dewan & Koss, 1989), such as the frequently irreversible tardive dyskinesia (TD) or sometimes fatal neuroleptic malignant syndrome. Several civil suits have been filed against psychiatrists for damages suffered as a result of TD (Simon, 1992), and the American Psychiatric

Association (APA) issued three cautionary reports about TD between 1979 and 1992, asking psychiatrists to use NLPs prudently. In 1990, congressional legislation limited and regulated the use of NLPs in nursing homes (Semla, Palla, Poddig, & Brauner, 1994).

Nevertheless, most clinicians today consider NLPs indispensable to treat psychotic disorders and it is very likely that a person diagnosed with schizophrenia will receive these drugs for months, years, or indefinitely. At the same time, there are numerous indications that NLPs remain unsatisfying to clinicians and insufficient for their main clinical purpose. Although lip service continues to be paid to the extraordinary antipsychotic properties of a course of acute treatment with NLPs, in recent practice in the United States over 80% of short-term hospital patients prescribed NLPs also have received other powerful central nervous system depressants, notably anticonvulsants and lithium (Baldessarini, Kando, & Centorrino, 1995).

The official date of the introduction in psychiatry of NLPs—1952—also marks the beginning of modern biological psychiatry.[1] No class of drugs before or since has provided such impetus to clinical and experimental investigation in psychiatry or triggered such far-reaching changes in the organization of mental health services. Today, the near-universal consensus on NLPs is that they are "antipsychotics," uniquely and specifically suited to treat schizophrenia: "Conventional neuroleptic agents have, since the mid-1950s, proven to be the most consistently effective compounds in the treatment of acute and chronic schizophrenic patients" (Wirshing, Marder, Van Putten, & Ames, 1995, p. 1259). The consensus is said to rest on solid scientific and clinical justifications: "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).

This view deliberately ignores much conflicting evidence, to be presented here. Worse, it implies that to question the usefulness of NLPs may relegate one to the fringe of scientific credibility (see accounts by Karon, 1989; Mosher & Burti, 1989; Ross & Pam, 1995). This may discourage critical inquiry by researchers and clinicians embarking on their careers (Kemker & Khadivi, 1995). Just as damaging, the prevailing consensus is acultural, failing to explain why NLPs are conceptualized quite differently in Europe than in America. Nor can it account for replicated findings from

[1] Earlier dates have been proposed: 1931, when the purified extract of rauwolfia serpentina, later known as reserpine, was tested on inmates of Indian insane asylums (Frankenburg, 1994); 1943, when Albert Hoffman discovered the hallucinogenic effects of LSD (Strassman, 1995); 1949, when William Cade hypothesized and then described the sedating effects of lithium salts on psychotic patients.

the World Health Organization cross-cultural schizophrenia studies showing that patients from developing countries, where only 16% were prescribed NLPs most or all of the time, had a significantly better outcome than patients from developed countries, with 61% on NLPs (de Girolamo, 1996; Jablensky, 1987).

The current consensus is also ahistorical, blind to serious doubts raised periodically about the enterprise of NLP drug treatment. The doubts are distracted away by "pragmatic" concerns about the control of "dangerous mental patients" (Klitzman, 1995), by the "unfeasibility" of nondrug alternatives requiring changes in philosophies and methods of service delivery, or by new "discoveries" confirming that treatment success only requires newer, better drugs (Kerwin, 1994). Invariably, the compromise is disillusioning because it fails to come to terms with the basic deficiencies of NLP treatment of seriously disturbed persons.

For example, after the first APA report on TD estimated that 20% of psychiatric patients showed "more than minimal signs of the disorder" (Baldessarini et al., 1979), the positive consensus about NLPs began to strain. After a few isolated reports the previous decade in the United States describing profound iatrogenesis, the "behavioral toxicity" of NLPs came to be squarely discussed by the APA and by leading clinical psychopharmacologists (e.g., APA, 1985, 1992; Gualtieri & Sprague, 1984; Van Putten & Marder, 1987). Few clinicians could feel unperturbed by the suggestion that NLPs had created, in the words of one well-known critic, "an epidemic of neurologic disease . . . among the worst medically-induced disasters in history" (Breggin, 1983, p. 109)—an opinion echoed in the pages of the *American Journal of Psychiatry* (Appelbaum, Schaffner, & Meisel, 1985). Even Pierre Deniker (1986), who introduced chlorpromazine in psychiatry with Jean Delay, published an article entitled "Are the Antipsychotic Drugs to Be Withdrawn?" (Deniker answered his question in the negative.)

Early in the 1990s, the doubts gave way to optimism about the treatment of schizophrenia, due to the marketing of new or formerly shelved compounds such as risperidone and clozapine, or the expected introduction of other "atypical" NLPs (olanzapine, remoxipride, sertindole, etc.). These are stated to be equal or superior to the older (conventional or classical) NLPs, especially for "neuroleptic nonresponsive" patients, but to produce fewer toxic effects. The latter are of extreme importance. In Wirshing et al.'s (1995) assessment of NLPs quoted earlier, immediately after the glowing evaluation of antipsychotic effectiveness, a number of caveats appear:

> This efficacy [of conventional NLP agents], though, has come at the cost of a number of untoward neurological side effects. Prominent among these are disturbances of the extrapyramidal system including dystonia, tremor,

> akinesia, bradykinesia, rigidity, akathisia, and a variety of tardive dyskinetic (TD) syndromes. These side effects have been linked to notorious patient noncompliance and iatrogenic morbidity. Additionally, conventional neuroleptics have been shown to be only partially effective at ameliorating the psychosis which contributes to persistent disability, subjective distress, and family burden. Finally, a substantial minority of patients derive little if any benefit from drug treatment. (p. 1259)

When risperidone was introduced in North America, its advertisement in the April 1994 issue of the *American Journal of Psychiatry* stated, "Incidence and severity of extrapyramidal symptoms (EPS) were similar to placebo." Almost identical statements have been made for soon to be introduced NLPs such as olanzapine and sertindole (Neergard, 1996). Such pronouncements may have a powerful impact. It matters little that later evaluations of the new drugs in ordinary clinical settings with ordinary patients may greatly modify the original enthusiastic assessments. For example, within one year of its introduction, risperidone—only the second NLP approved by the Food and Drug Administration in 20 years—became the second most used NLP in some hospitals. In one institution, Carter et al. (1995) found that its use spread far beyond the population of adult schizophrenics, the only one for whom efficacy data were available. In fact, the cost of risperidone alone exceeded the amount spent on *all* NLPs during the preceeding year. However, in that ordinary setting, risperidone did not show less toxicity than haloperidol, and the mean drug dose at which toxic effects appeared was distinctly lower than that suggested by data from premarketing clinical trials. With each passing year, risperidone presents itself as less and less "atypical": As of this writing, several published reports have implicated this drug in the production of quintessential neuroleptic effects such as TD and neuroleptic malignant syndrome (Buzan, 1996; Dave, 1995; Singer, Richards, & Boland, 1995; Woerner, Sheitman, Lieberman, & Kane, 1995). Yet, less than three years after its market approval and with no published data on long-term effects, risperidone became in October 1996 the most widely prescribed NLP in the United States (Neergard, 1996).

The reception given clozapine—the first atypical NLP, from the benzodiazepine family, introduced in North America in 1990—is equally informative. Modestly used in Europe since the early 1960s, clozapine had its use greatly restricted after about 20 people died from it, due to agranulocytosis (sharp drop in white blood cells) in 1975 in Finland and Switzerland (Kerwin, 1994). 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). Clozapine was also described as being free of EPS: Its advertisement 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 stated simply that clozapine "does not cause extrapyramidal effects" (Schwartz & Brotman, 1992, p. 981). By 1993, however, as D. Cohen (1994a) reviewed, clozapine had been associated—in over a dozen open and blind studies—with tremor, akathisia, tardive dyskinesia, neuroleptic malignant syndrome, as well as other typical NLP effects. Relative to other NLPs, the frequency of clozapine-induced EPS was typically lower, but the findings were unmistakably clear. Yet, even after these reports appeared, one could read in no less a publication than *The New England Journal of Medicine:* "Unlike classic neuroleptic agents, *clozapine is not associated with the development of acute extrapyramidal symptoms* [italics added]" (Alvir, Lieberman, Safferman, Schwimmer, & Schaff, 1993, p. 162).

Skelton, Pepe, and Pineo (1995) undertook a meta-analysis of 11 studies to derive a quantitative estimate of the magnitude of clozapine's effect on patient symptoms, relative to other NLPs. In eight studies that used the Brief Psychiatric Rating Scale (BPRS) to rate psychopathology, the average symptom score was improved by 26 percentile points. Skelton et al. state that this suggests that "the comparative effect of clozapine over other antipsychotic medications may be regarded as moderate to large" (p. 276), but one should accept this finding with caution. One difficulty may arise because BPRS symptom ratings often correlate positively with EPS (Baldessarini, Cohen, & Teicher, 1988; D. Cohen, 1989; Halstead, Barnes, & Speller, 1994). For example, elevated scores on BPRS items such as "tension/anxiety" and "emotional withdrawal" may actually reflect EPS such as akathisia and parkinsonism. Given that EPS would probably have been lower in patients on clozapine, this could result in improved BPRS scores for these patients compared with patients on conventional NLPs. Also, although observer expectancies and "unblinding" in clinical trials may have a powerful impact on drug effect ratings (Double, 1995; Greenberg, Bornstein, Greenberg, & Fisher, 1992; White, Kando, Park, Waternaux, & Brown, 1992), only a single study described how observers were kept unaware of patients' treatment conditions. Finally, in only 2 of 11 studies were patients studied more than 2 months. Of course, these methodological features are not limited to the literature on clozapine.

Yet, 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 biopsychiatric idea that

"schizophrenia" represents a genetically predisposed, environmentally triggered, neurodevelopmental brain disease which, at this state of our knowledge, best responds to chemical intervention.[2] According to 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" (p. 344). Indeed, no biological dimension specific to schizophrenia has yet been charted (Chua & McKenna, 1995; Pam, 1995).

From where does the continued use of NLPs derive legitimacy? Possibly the first reason may be the natural desire to bring under quick control the seemingly inexplicable, disturbed, and disturbing behavior and moods displayed by a psychotic individual. Yet, the use of NLPs extends far beyond this limited indication, commonly encompassing lifelong medication for individuals who have been hospitalized on more than two or three occasions and raising questions about the extent to which chronicity in schizophrenia results from a system of "care" in which all interventions remain secondary to ensuring that the schizophrenic takes his or her medication. According to Kuhn (1970), the inertia of a scientific system is such that it can remain in a dominant position even after it is seen as *generating* the problems which necessitate alternative formulations. Support for an inefficient system comes mostly from extrascientific factors, which Karon (1989) hinted at in his conclusion of a detailed review of medication versus psychotherapy studies: "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]" (p. 146). According to Ross (1995), several psychological strategies help erroneous logic keep hold in biological psychiatry: "The conceptual system of biological psychiatry is organized [such that the] tautologies, positive feedback loops, closure to alternative hypotheses, pervasive overgeneralization, use of dissociation to eliminate cognitive dissonance, and other structural and functional properties of the system maintain it in a dysfunctional homeostasis" (p. 127).

This appraisal of NLPs begins with early descriptions of their effects on psychiatric patients. These reports were stated in graphic terms that have virtually disappeared from the contemporary literature and focused on psychic indifference and abnormal movements, viewed as the sine qua non of NLPs' therapeutic action. By the late 1970s, despite the absence of any new or pertinent experimental, clinical, or epidemiological evidence,

[2]For different views on the nature of schizophrenia, see Boyle (1990), Carson (1991), Sarbin (1990), and Wiener (1991), among others.

most researchers in North America (but not in Europe) appeared to have rejected this view.

PSYCHIC INDIFFERENCE: THE FIRST CLINICAL EFFECT OF NEUROLEPTICS

Accounts and reminiscences of pioneers of clinical psychopharmacology suggest that NLPs gained favor in the hospital psychiatry of the 1950s because of the drugs' outstanding ability to stupefy agitated inmates as well or better than electric shock, insulin coma, and lobotomy (D. Cohen, in press). Most contemporary writers fail to appreciate that NLPs were entirely tried, evaluated, and found to be beneficial *within the institution,* where they coexisted harmoniously with convulsive treatments for a full decade, until society began to turn to noninstitutional solutions to manage the problems posed by dependent psychiatric populations (Gronfein, 1985).

Heinz Lehmann (1989, 1993), the first North American to publish an article on administering chlorpromazine (CPZ) to psychiatric patients (Lehmann & Hanrahan, 1954), reminds us that in the 1940s, "Our two major therapies were insulin-induced hypoglycemic coma and electroconvulsive shock therapies (ECT) for schizophrenia and affective disorders. . . . Paraldehyde and the barbiturates were about our only means to quell agitation and violence in addition to physical seclusion and restraint. . . . 70% to 80% of [patients] relapsed" (1993, p. 294). Lehmann therefore experimented with procedures "that would be impossible to repeat today" (p. 295). He describes "brain biopsies" done on randomly selected patients; "carbon dioxide treatment"; the use of "very large doses of caffeine" in stuporous catatonic schizophrenics, "of course with no results"; nitrous oxide "to the point where there was complete loss of consciousness"; injections of sulphur in oil and typhoid antitoxin, both of which only produced high fevers; injections of "turpentine into the abdominal muscles which produced—and was supposed to produce—a huge sterile abscess and marked leucocytosis" (1989, p. 263); etc. Lehmann's account illustrates the notion that, in devising experiments for their forgotten and socially devalued wards, asylum doctors had little incentive to choose treatments causing least harm.

The treatment of psychiatric patients with CPZ used alone, at Ste-Anne Hospital in Paris, was first reported by Delay and Deniker in May 1952. However, the very first psychiatric use of CPZ alone occurred on November 9, 1951, when Leon Chertok injected an unspecified intravenous dose of the drug into Cornelia Quarti, a 28-year old psychiatrist, and voice-recorded her comments (Chertok, 1982). Previously, Laborit (1967) had reproduced Quarti's own written account. Some excerpts:

> I begin to feel that I am getting weaker and weaker, it is very difficult and harrowing. At 12h10, one of the assistants tries to . . . hypnotize me. I gather all my energies to shout at him (so it seems to me): "No, you are bothering me." In fact, [judging from the voice recording, I] transmitted a weak and monotonous voice. . . . At 13h . . . the painful feeling of imminent death gives way to a euphoric calm. I still feel I am dying, but this leaves me indifferent. . . . At 15h, . . . my speech has become painful, dysarthric, I can't find my words. . . . In the evening, I am still very tired and must stay in bed . . . The speech difficulty continues. . . . The lassitude and speech disorders persist for a few days to disappear progressively. (pp. 7168–7169)

In the first British report on CPZ in psychiatry, Anton-Stephens (1954) identified psychic indifference as "perhaps the characteristic response to chlorpromazine. Patients responding well to the drug have developed an attitude of indifference both to their surroundings and their symptoms best summarized by the current phrase 'couldn't care less'" (p. 544). Inevitably, these effects led the original investigators of CPZ to make formal connections with lobotomy or leucotomy, which produced a "frontal lobe syndrome" characterized by apathy, loss of initiative, indifference to environmental and bodily stimuli and impairment of sophisticated intellectual functions such as the ability to plan ahead (Stuss & Benson, 1986).

Freyhan (1955) explained that "the first hypothesis advanced by French authors for the action of chlorpromazine . . . assumed a synaptic interception between the cortex and the diencephalon, resulting in suppression of excitations. This 'chemical lobotomy' theory . . . has since appeared in various reports" (p. 72). Lehmann (1989) actually acknowledged that the idea to administer CPZ came to him because he thought the new drug might produce the effects of lobotomy: "I thought [CPZ] was just another nonbarbiturate sedative. But there was a certain statement [in the new literature by Delay and Deniker]: it acted like a 'chemical lobotomy,' which puzzled me, and I said to myself, there is something more to it" (p. 264). In his second article on CPZ, Lehmann (1955) observed, "Chlorpromazine is of value in the treatment of pain associated with terminal carcinoma. The effect in these cases is probably similar to that observed following a frontal lobotomy" (p. 94). Anton-Stephens (1954), referring to two patients who, upon receiving the drug, became "mute," "dazed," and "incontinent," but "showed no concern over this," wrote: "The picture they presented and that sometimes encountered following a pre-frontal leucotomy was independently made by several observers" (p. 549). In a paper on parkinsonian symptoms produced by CPZ, the French psychiatrists Letailleur, Morin, and Monnerie (1956) suggested these symptoms amounted to "functional lobotomy" (p. 806). Hans Steck (1956), a noted Swiss neuropsychiatrist, was more explicit. Discussing motor disorders arising during CPZ treatment, he concluded as follows:

> Here again it seems important in order to localize the [effects of] neuroleptics to highlight the common traits and the distinctive traits of the effect of leucotomy and the action of Chlorpromazine. In both cases we witness the appearance of passivity, a reduction of psychic tension, stimulation and initiative . . . But this occurs with leucotomy with no one ever having described a parkinsonian syndrome, whereas with the new treatment it appears almost obligatory. (p. 789)

NEUROLEPTIC EFFECTS AND EXTRAPYRAMIDAL SYMPTOMS: FIRST IMPRESSIONS

The "almost obligatory" parkinsonian syndrome and other motor disorders arising during NLP treatment were first reported by Steck (1954). He noted parkinsonism and akathisia in 37% of 299 patients treated with CPZ or reserpine. At Vermont State Hospital, Brooks (cited in Goldman, 1955, p. 51) estimated that "all patients who are on large doses of Thorazine—for any length of time show signs of basal ganglion dysfunction." Similarly, at Pilgrim State Hospital, New York, Pleasure stated, "Probably two-thirds of our patients showed some degree of Parkinson-like symptoms" (cited in Goldman, 1955, p. 55). Lehmann (1989) remembers that when he first noticed CPZ-treated patients with typical symptoms of Parkinson's disease, "... it did not seem possible because at that time there was no such thing as drug-induced Parkinsonism; there were no models known in animals or humans of induced Parkinsonism, known only were the post-encephalitic or the spontaneous, idiopathic Parkinsonism, yet this looked very much like it" (1989, p. 265).

Steck (1954) was the first to note the similarities between the drug-induced effects and encephalitis lethargica (EL) or von Economo's disease, which he knew well. An epidemic of EL, thought to be of viral origin, swept through Europe from the mid-1910s to late 1920s, killing hundreds of thousands of people and leaving others afflicted with permanent parkinsonism and dementia.[3] Steck pointed to the initial sedation produced by CPZ and

[3] Boyle (1990, especially pp. 65–71) argues that the populations studied by Emil Kraepelin (who coined "dementia praecox") and Eugen Bleuler (who coined "schizophrenia") in the late 1800s and the populations studied by von Economo (who authored the classic description of encephalitis lethargica) in the early 1900s had many striking similarities. According to Boyle, although encephalitis lethargica had not yet been identified, "there are at least good circumstantial grounds for supposing that [Kraepelin and Bleuler] were for the most part dealing with the consequences of some forms of encephalitic infection and that at least a sizeable minority of their patients would later have been diagnosed as cases of post-encephalitic Parkinsonism" (p. 69). As these neurological diseases became rarer and as psychiatry and neurology evolved into two separate disciplines, the referents of "schizophrenia" changed until that diagnosis "came to be applied to a population who bore only a slight, and possibly superficial, resemblance to Kraepelin's and Bleuler's"

reserpine and the initial lethargy of the encephalitis, followed in both cases by a parkinsonian syndrome, except that the new drugs seemed to "speed up" the process observed in cases of EL. He suggested that the upper brain stem and extrapyramidal system, where EL had been shown to produce its pathology, were the new drugs' site of action. In Germany, Haase (1958, 1961) reported similar findings dating from 1954. Just like Steck, he likened the drug effects to a "speeded-up film version" *(tempo cinématographique accéléré)* of EL.

Delay and Deniker also made connections between the drug effects and the encephalitis. Deniker (1989) recounts that he and his colleague were asked by the French military to explain the occurrence of "dyskinetic episodes" among soldiers undergoing disembarkation exercises (and receiving prochlorperazine as an antiemetic):

> ... Delay and I found the explanation. He remembered that similar episodes had been observed during epidemics of encephalitis lethargica following the first World War, and I actually found a number of references thereto in the literature. . . . *All the side effects of neuroleptics had already been described between 1920 and 1935 as a sequelae of encephalitis. . . . With this medication one obtained with progressive doses all the syndromes of encephalitis from the initial akinesia without hypertonias up to a hyperkineto-hypertonic syndrome which preceded the tardive dyskinesias* [italics added]. Moreover, corresponding to each neurologic syndrome there were particular psychological changes, independent of the prior mental state of the patient: for example, indifference with akinesia, mental depression with Parkinsonism, impatience with the hyperkinesias. (Deniker, 1989, p. 255)

Delay and Deniker therefore formally proposed in 1957 the word "neuroleptic" ("which takes hold of the nerve") to formally define CPZ and related compounds. It included five characteristics: (a) creation of a special state of psychic indifference, characterized by a hypersomnia reversible with ordinary stimuli, reduction of spontaneous and provoked motor activity, inhibition of conditioned reflexes and of learning; (b) efficacy in sedating excitation, agitation, manic states and agressive and impulsive outbursts; (c) gradual reduction of acute and chronic psychotic disorders; (d) production of extrapyramidal and vegetative syndromes (paroxystic dyskinesias, parkinsonian syndrome and pathology of the postencephalitic parkinsonism kind: akinesia, hyperkinesia, hypertonia; modification of

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p. 70). This occurred because the "validity" of schizophrenia was taken for granted, and because a shift to *behavioral* diagnostic criteria did not seem problematic to a profession "claiming jurisdiction over both disturbing behaviour and disturbing neurology" (p. 70). Boyle's thesis could explain why Kraepelin and Bleuler described cases that resemble TD, more than half a century before NLPs were introduced.

thermal regulation, of pulse, of blood pressure, of secretions, of metabolism); (e) dominant subcortical effects, accounting for the preceding neurological effects (see Delay & Deniker, 1961).

This definition helped crystallize a consensus that had formed soon after the introduction of CPZ, and which probably found its clearest expression in Denber (1959): "The ability to induce an extrapyramidal action is a *sine qua non* of therapeutic effectiveness" (p. 61). As a result, some psychiatrists wondered "whether we should consider deliberately producing basal ganglion symptoms in patients [in order to] produce a higher improvement rate" (Ayd, cited in Goldman, 1955, p. 57). Other clinicians, such as Flügel (1956), wrote: "We busied ourselves to produce these states [of parkinsonism and psychic disinterest] systematically through continuous treatment with Reserpine and Chlorpromazine. . . . Approximately half the patients [were] completely immobile. One could move them about like puppets" (pp. 790–791).

Were long-term negative effects considered? Steck (1956) asked "whether we were making our patients run the risk of contracting a severe illness, a chronic and incurable parkinsonism" (p. 787). Because of instances where EPS had disappeared after NLP withdrawal, Steck felt that the risk was minor—although early on, he and several others described cases of attenuated or full-blown extrapyramidal syndromes persisting in patients one full year after the cessation of NLP treatment (Delay, Deniker, Bourguignon, & Lempérière, 1956; Ey, Faure, & Rappard, 1956; Schöneker, 1957).

Interestingly, antipsychotic attributes of NLPs were third on Delay and Deniker's list. It is easy to imagine that once the psychotic individual became indifferent, verbally and physically withdrawn, and less excited, the "psychosis" would also be seen as "gradually reduced." As Lehmann (1993) writes, early clinicians did not impute antipsychotic properties to NLPs until several years after the drugs were in use: "Even in my correspondence with other clinicians in the United States working with the phenothiazines neither I, nor they, dared to attribute specific antipsychotic effects to these new drugs. In 1956, . . . I introduced the term 'antipsychotic' apologetically, and more as a metaphor than a designation" (p. 300).

I have cited extensively from the early clinical literature on NLPs to suggest that most contemporary writers display a blind spot about NLP toxicity. Recent textbooks of psychopharmacology and countless studies of the NLP treatment of schizophrenia might not contain a single mention of psychic indifference, the outstanding NLP effect. Suggestions that NLP effects mimic those of a serious infectious neurological disease or that NLP treatment and lobotomy may produce similar effects are rarer still, if nonexistent. Proceedings from the First International Meeting on the

Neuroleptic-induced Deficit Syndrome (NIDS) (Lader & Lewander, 1994) provide a telling example. Although NIDS appears clinically indistinguishable from the frontal lobe syndrome produced by lobotomy and characterized by apathy, disinterest, and lack of initiative, none of the published papers from this 1993 symposium mention lobotomy or encephalitis lethargica, including the one paper (Lewander, 1994) purporting to review Delay and Deniker's observations of CPZ-induced sedation, apathy, and indifference.

This blind spot also means that contemporary researchers erroneously report various NLP-induced phenomena as new clinical observations. For example, in tying particular mental states to particular abnormal involuntary movements, Delay and Deniker spelled out a full theory of the behavioral toxicity[4] of NLPs, 30 years before Van Putten and Marder (1987) published an article on that topic (also omitting to mention Delay or Deniker). Several papers have rediscovered that NLPs regularly induce dysphoric mental states, singly or jointly with EPS such as akathisia and dystonia (Halstead et al., 1994; Lewander, 1994; Newcomer et al., 1994; Thornton & McKenna, 1994; Young, Stewart, & Fenton, 1994). Thornton and McKenna (1994) actually emphasize similarities with postencephalitic parkinsonism; not to suggest that NLPs mimic that disease but, in a leap of unjustified biological reductionism, to advance that all "psychiatric" phenomena are really "neurological" phenomena.

Breggin (1983, 1993) stands out among contemporary writers for his use of early clinical observations to understand the nature of NLP action. He has suggested that psychic indifference reveals NLP-induced "deactivation," which "designates a continuum of phenomena variously described as disinterest, indifference, diminished concern, blunting, lack of spontaneity, reduced emotional reactivity, reduced motivation or will, apathy, and, in the extreme, a rousable stupor" (1993, p. 9). According to Breggin,

[4]Lehmann (1979) defined behavioral toxicity as the harmful modifications of behavior resulting from specific or nonspecific drug action. Summerfield (1978) dates first mention of the concept to 1956, as a result of attempts to minimize undesirable effects of the newly discovered NLPs. Although Summerfield does not otherwise discuss NLPs, he provides valuable insights to understand and evaluate NLPs' characteristic psychological effects:

> Among the first effects [of drug-induced toxicity] are visible changes in behaviour. A very serious consequence is loss of self-critical monitoring of whatever one may be doing . . . impaired in the particularly dangerous way that the person concerned is unaware of the process of behavioural deterioration to which he or she is being subjected. . . . (H)igh-level psychological functions may be the first to go under the stress of poisons and pollutants. . . . Only therefore by looking for impairments of functions immediately dependent upon the highest levels for their control and coordination might any adverse effect be detectable at all. It is a profound conceptual issue that has spent more time in oblivion than in recognition. (pp. 336–337)

deactivation is the essence of what is termed the "antipsychotic effect" (and of the lobotomy effect). Reviewing clinical and physiological parallels between NLP effects and characteristic symptoms of encephalitis lethargica, Breggin (1993) notes insightfully that, aside from previous NLP exposure, nothing could differentiate an acute, severe attack of encephalitis from an attack of NLP malignant syndrome. This suggests clear lines of investigation, especially since the ultimate neurocognitive sequela of the encephalitis was dementia. After a flurry of articles in the 1980s (see section on Tardive Dementia and Tardive Psychosis), the issue of whether NLPs produce dementia after prolonged use or as a further deterioration of TD has mostly faded from discussion. However, this may be the start of another cycle of official discontent with NLPs. In several published reactions to a review (Hegarty, Baldessarini, Tohen, Waternaux, & Oepen, 1994) finding that outcome in schizophrenia is not better now than it was early in the century, it is suggested that NLPs may be responsible, by producing or worsening negative symptoms, deficit syndromes, and Alzheimer-type cerebral pathology (Dean, 1995; Oken & McGeer, 1995; Warner, 1995). More recently, in a longitudinal study of 71 subjects with dementia, McShane, Keene, Gedling, Fairburn, Jacoby, and Hope (1997) found that the mean decline in cognitive score in the subjects who took NLPs was twice that of the patients who did not. Furthermore, in the former subjects, the start of NLP treatment coincided with faster cognitive decline: the median rate of decline was 5 points per year before treatment and 11 points per year after that.

APPRAISING CURRENT USE OF NEUROLEPTICS

The following sections provide a review covering current use of NLPs. When considering one topic, such as dosage, it becomes necessary also to discuss EPS, therapeutic effectiveness, response rate, clinical practice styles, and so forth. Some repetitions are thus unavoidable. The remainder of this chapter focuses on a few topics that cover a broad sample of the literature and highlight key problematic areas.

The Question of Dose

After one is reasonably convinced that a drug should be prescribed to treat an undesirable condition, the first issue to consider is determining the appropriate dose. Today, the results of dose-response studies in humans and animals are available prior to the marketing of a given medication and dosage recommendations within generally narrow ranges are made to physicians by drug manufacturers.

However, after more than 40 years of research and clinical experience with NLPs, NLP dosages are not well mapped nor are patients' drug responses predictable. Furthermore, although NLP use is associated with several *dose-dependent* toxic effects, the minimum effective dosages of various NLPs are unknown. The phrase "minimum effective dosage" is that which the most authoritative NLP prescription guidelines recommend that clinicians prescribe in long-term NLP treatment (APA, 1992, p. 251). These guidelines—which focus on minimizing the risk of TD—are not universally accepted and have no *official* standing. As late as 1995, McIntyre and Simpson could write, "It would be helpful for practitioners if there were some sort of protocol to guide one through neuroleptic use" (p. 135).

The confusion over NLP dosage, in theory and in practice, highlights several of the general problems plaguing the overall use of NLPs. An obvious difficulty is that although dozens of studies specify a dosage range below which no "therapeutic" response is observed and above which toxicity appears unacceptable (to clinicians) and/or therapeutic efficacy does not increase, this range is rarely respected in clinical practice. The scientific consensus during the current decade holds that dosing above 10 mg/day of haloperidol (HPL) equivalents improves neither the speed nor the degree of therapeutic response in the vast majority of cases (Baldessarini et al., 1988; Dewan & Koss, 1995; McIntyre & Simpson, 1995). Data from controlled clinical trials, reinforced by comprehensive meta-analyses and continually endorsed by leading clinical psychopharmacologists, indicates that a dose between 3 and 7 mg/day of HPL equivalents suffices to maintain the full desired "antipsychotic" effect (Bollini, Pampallona, Orza, Adams, & Chalmers, 1994; Hogarty, 1993; McEvoy, Hogarty, & Steingard, 1991).

Yet, the majority of studies of prescription practices show mean daily doses far exceeding the range's upper limit (see, e.g., Peralta, Cuesta, Caro, & Martinez-Larrea, 1994; Reardon, Rifkin, Schwartz, Myerson, & Siris, 1989; Segal, Cohen, & Marder, 1992; Volavka et al., 1990). This "tendency for psychiatrists everywhere to use higher doses of antipsychotics than necessary . . . is true even more so in the United States than elsewhere" (McIntyre & Simpson, 1995, p. 135). Baldessarini et al. (1995) report a contrary finding from a Boston-area private teaching hospital: mean doses in 1993 were just under 5 mg/day in HPL equivalents. These investigators observed similar dosages at the same hospital in 1989 and believe their findings reflect a downward trend characterizing this decade. However, until confirming evidence is available, the findings may be considered an anomaly. Although clozapine was prescribed at a mean dose of 331 mg/day in that Boston study, it was prescribed the same year at a mean dose of 591 mg/day in a New York City hospital (Pollack et al.,

1995). This interstate variation in the dosing of clozapine—an NLP whose potential to induce the sometimes fatal agranulocytosis appears dose-dependent and whose prescription legally requires extremely close monitoring—suggests strongly that even wider variations still exist with respect to other, more widely used NLPs. One simply needs to compare daily doses from any number of published studies selected at random in the psychiatric literature or from surveys of practicing psychiatrists. D. Cohen and Bisson (1997) surveyed 350 Canadian psychiatrists; less than 2% indicated that a 20 mg/day dose of HPL for maintenance treatment for an adult or elderly chronic patient was too high or excessive. Meise, Kurz, and Fleishhacker (1994) surveyed Austrian psychiatrists and found a 50-fold difference between the lowest and highest recommended doses for NLP maintenance treatment (40 to 2,000 mg/day in CPZ equivalents).

Daily doses above 1 or 2 gm of CPZ equivalent are rarer nowadays, although it has been frequently observed that "high-potency" NLPs (such as haloperidol and fluphenazine) are prescribed in higher CPZ-equivalent doses than "low-potency" NLPs (such as CPZ and thioridazine). In CPZ-equivalents, Baldessarini, Katz, and Cotton (1984) found a high- to low-potency dose ratio of 3.5:1 in a sample of 110 Boston-area patients; Segal et al. (1992) reported a 5.3:1 ratio among a sample of 243 California sheltered-care residents. Many explanations have been given for this phenomenon, including clinicians' preference for managing adverse effects typical of high-dose, high-potency treatment (i.e., EPS) rather than toxic systemic syndromes produced by high-dose low-potency NLPs; ease of increasing high-potency doses if patients show little improvement. Dewan and Koss (1995) offered another explanation: large variance in the NLP equivalencies found in psychiatric manuals! These authors compared equivalency tables in a dozen manuals and found significant disagreement on the clinical equivalence of some NLPs, with up to 500% variance reported in texts. Most affected were the high-potency drugs. For example, two texts stated that 100 mg of CPZ were equivalent to 1 mg of HPL and two texts to 5 mg of HPL. Thus, "[an acutely psychotic] patient could be prescribed 5 mg of haloperidol daily or 25 mg daily by two different physicians who each thinks he is prescribing the appropriate minimum" (p. 231).

Classifying NLPs according to "potency" and determining their clinical equivalence with respect to a standard drug or each other is a mostly North American custom. Dewan and Koss (1995) can only include American texts in their review. In France the idea of high- and low-potency NLPs or of clinically equivalent doses of chemically different NLPs has no currency. It is not mentioned in the latest edition of that country's

authoritative psychopharmacology manual (Ginestet & Kapsambelis, 1996), which still manages to describe seven different ways to classify NLPs. Generally, French authors believe that each NLP has a unique profile of up to six main clinical effects, even that different doses of the same NLP will produce quite different profiles. How seriously this notion is taken in American psychiatry is illustrated in a comment by Johns, Mayerhoff, Lieberman, and Kane (1990): "On a clinical level, there is certainly some feeling, based largely on anecdotal evidence, that some patients do better on one drug than another." Johns et al. do acknowledge, "Remarkably, there are very few reports in the literature that address this issue in a systematic fashion" (p. 58).

As mentioned, another difficulty related to NLP dosage is predicting clinical response to various fixed doses. More often than not, typical NLP effects will be more visible to outside observers at "moderate" or "higher" dosages. Yet one would expect that the field would have gone substantially beyond such a commonsense notion, given the energies, talents, and sums invested in NLP psychopharmacology since the 1950s. For example, in a study by Rifkin, Doddi, Karajgi, Borenstein, and Wachspress (1991), newly admitted inpatients with a diagnosis of schizophrenia were randomly assigned to receive either 10, 30, or 80 mg/day of HPL (at the time of the study, 20–25 mg/day was considered a "standard dose"). Subjects were then evaluated under double-blind conditions for 6 weeks. At the end of this period, no differences in clinical condition—and no differences in EPS—were noted between the three groups. More recently, Stone, Garver, Griffith, Hirschowitz, and Bennett (1995) also found no differences in clinical response between 4, 10, and 40 mg/day of HPL administered over a 2-week period. To be sure, other studies arrive at different results. Van Putten, Marder, and Mintz (1990) compared 5, 10, and 20 mg/day of HPL in the treatment of acute psychosis, finding an advantage for 20 mg at 1 week, but a clear deterioration because of "psychotoxicity" at 2 weeks, with 10 mg more effective overall and 5 mg effective for some patients. Stone and Garver (1996) insist that, given the state of knowledge, studies are needed to test the effectiveness of doses of HPL including 0 and 1 mg/day.

Minimum effective NLP dosages have not yet been determined, nor have investigators been able to demonstrate, even with the most sophisticated fixed-level blood studies, the existence of therapeutic plasma levels of NLPs (Kane, 1989; Simpson & Yadalam, 1985; Stone & Garver, 1996). Waddington, Weller, Crow, and Hirsch (1992) stated, "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). Bitter,

Volavka, and Scheurer (1991) more directly summarized the state of the art of NLP dosing: "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).

If prescribing high doses of NLPs does not lead to improved clinical results, yet clinicians persist in prescribing high doses, one may turn one's attention to extraclinical influences on the prescribing situation. Referring to American high dosing, McIntyre and Simpson (1995) believe that it results partly from "the wave of managed health care engulfing psychiatry" and pressures from "third-party payers to do more and to do it faster. Psychiatrists . . . may find themselves changing their clinical techniques in order to accommodate these demands" (p. 135). Undoubtedly important, these recent economic pressures cannot account for the high-dosing phenomenon, which well antedates them.[5]

The inability to determine minimal dosages or to prescribe within dosage ranges recommended in the research literature raises fundamental questions about the ability of clinicians and researchers to make sense of their observations (an ability which may be mostly context-dependent). For example, Pollack et al. (1995) observed that, after 12 weeks of treatment, Austrian psychiatrists prescribed clozapine to their patients at a mean dose of 153 mg/day, compared with 458 mg/day for American psychiatrists. Yet, symptom ratings similar at baseline for both groups of patients had decreased significantly more in absolute and relative terms in the Austrian cohort by the 6th week and stayed lower through the 12 weeks of the study. Despite the sizable body of findings showing diminishing return with increasing dosage, the association of greater benefit with lower dose was characterized by Pollack et al. as "surprising," an "anomaly" (p. 315). Such "resistance" indicates that actual, observed clinical results weigh less in NLP use and evaluation than ingrained practice habits. More important, it suggests that the treatment zeitgeist may actively bias clinicians in favor of NLPs, influencing them to disregard essential information

[5] According to Deniker (1990), "As early as 1956, the question of why dosages were higher in America than in Europe was posed. Denber was appointed by New York State and by [Smith Kline & French] Company to investigate the reason. The answer was simple: American psychiatrists were more hurried than their European colleagues" (p. 84). Just how hurried the former were is indicated in this comment by Kinross-Wright, a Houston psychiatrist, who was asked during the first major symposium on CPZ in the United States, in 1955, why he used doses as high as 4,000 mg a day: "Well, the reason we haven't given more than 4,000 mg (actually, it is 4,800 mg now) is because we don't like to subject patients to more than 40 tablets a day. We think that is just about the limit. The reason we go so high is that in our intensive scheme of treatment we just keep pushing up the dosage until the patient shows definite signs of clinical improvement" (cited in *Chlorpromazine and Mental Health*, 1955, p. 68).

with critical bearing on their own prescribing behavior, their patients' clinical outcomes, and their judgment on the overall value of NLPs. This is also evident in the literature touching on the effectiveness of NLPs.

THE EFFECTIVENESS OF NLPS IN THE ACUTE AND LONG-TERM TREATMENT OF SCHIZOPHRENIC DISORDERS

Zito and Provenzano (1995) distinguish between the *efficacy* and the *effectiveness* of drug therapies. The first refers to "the health outcomes of a drug when it is used under ideal conditions," in a well-controlled environment, with compliant and homogeneous subjects. The second refers to "how well a drug works under usual practice conditions" (p. 737), administered by different types of clinicians in a spectrum of settings, to a heterogeneous population often receiving other drugs. In theory, this distinction is useful and partially explains wide differences in reported outcomes and direct costs of certain drug treatments (Carter et al., 1995). In practice, both types of evaluations are difficult to distinguish. A random-assignment, double-blind study may be conducted with a heterogeneous, noncompliant population. Or, a new drug may be tested in an open trial in an ordinary clinical setting, but the extra care and enthusiasm of the researchers may make the conditions "ideal" (for patients). True efficacy studies might only refer to some premarketing drug trials that aim to meet regulatory requirements. As a rule, for recently introduced drugs, more efficacy studies are available. In any case, most reviews mix efficacy and effectiveness studies together. In this chapter, the term *effectiveness* will refer to both types of evaluations.

AN EARLY NLP-PLACEBO COMPARISON

Two reports of placebo substitution of NLPs and antiparkinsonians raise intriguing, still unresolved questions bearing directly on the issue of effectiveness. During nine months of 1959, in a ward housing 68 chronic patients, French psychiatrist Serge Follin replaced the CPZ liquid preparations with an identical-looking placebo (Follin, Chanoit, Pilon, & Huchon, 1961). Aside from the hospital director, neither personnel nor patients were informed. The patients had been treated for a minimum of six months and a maximum of three years, at daily doses ranging from 150 to 700 mg. Although 29 of the patients were excluded from the analysis (they changed wards or received other treatments and no further information about them is provided), the results are still astonishing: Ward life remained completely unchanged and no one saw through the trick. Instances of patient misbehavior were neither less nor more common than before the placebo substitution. Various increases and decreases of

placebo doses were made by unknowing ward physicians: clinical notes show that insomniac patients were able to sleep when the dose was increased while others who appeared sedated became more agitated when doses were decreased. After nine months, the authors tallied their results: 22 patients (56.5%) rated as definitely improved (including 11 discharged), 15 (38.5%) rated as unchanged, two (5%) rated as worsened.

A second experiment is recounted by Lemoine (1995). In the early 1980s, also in France, worried about the indiscriminate prescription of antiparkinsonians to patients receiving NLPs in his hospital, Lemoine replaced, after one month of baseline observation, the antiparkinsonian drugs with identical-looking placebo gelules in one half (randomly chosen) of the ward patients. Only the ward director and the hospital pharmacist were aware of the subterfuge. None of the placebo-treated patients showed any appearance or worsening of abnormal movements. More to the point, medical personnel noted clinical improvement in patients on placebo, who then received lower NLP doses. Lemoine phrased his astonishment thus: "Without his [antiparkinsonian drug], a patient was improved and reduced his use of neuroleptics!" (1995, p. 174).

Because of current requirements for informed consent in research, it would be difficult to carry out such experiments today. Strictly speaking, the studies tell us more about the power of placebo than the effectiveness of NLPs or the confounding effects of antiparkinsonians. However, it is regrettable that such studies were not analyzed in greater detail or that systematic efforts are not made to replicate them with a view to augmenting placebo effectiveness—results might go a long way in dispelling much of the aura surrounding the efficacy of NLPs or, at the very least, in establishing more precise indications for these drugs.

Effectiveness Studies

To evaluate the effectiveness of NLP treatment of schizophrenia, studies since the 1950s have measured how often patients on medication and patients not on medication experience a relapse. Generally, two groups of comparable patients, one administered NLPs and the other a placebo, are followed for a determined period (usually 2 to 6 months, occasionally 12 months, very rarely up to 24 months) following release from an index hospitalization or psychotic episode. Effectiveness is evaluated by estimating, by means of appropriate statistical tests, whether the proportions of patients who relapse in each group differ significantly. There is no uniform way to define relapse: It may operationalized as a return to active medication, rehospitalization (if patients are living in the community), an exacerbation of symptoms that would qualify as an active episode of schizophrenia, a set increase (sometimes over a set period) in psychotic

symptoms as measured by a known rating scale, and so on. Although during the past decade the latter criterion is often used, there are no systematic reviews that have attempted to uncover differences in outcome of NLP treatment depending on definitions of relapse.

Approximately 1,300 NLP effectiveness studies have been published since the mid-1950s (Keck, Cohen, Baldessarini, & McElroy, 1989). The overall rate of effectiveness reported (see reviews by Baldessarini, 1985a; J. M. Davis, 1975) is similar to the rate recently estimated by J. M. Davis et al. (1993) from 35 random-assignment, double-blind studies involving 3,720 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 presumably would relapse even if they were on drugs, we obtain the "net" effectiveness rate of 34%. Put another way, for only one in three patients on NLPs who do not relapse during a set study period, NLP treatment appears to be the determining factor.

Numerous factors, internal and external to the individual, can be expected to trigger, provoke, or influence a relapse (or, inversely, a state of "clinical stability"). Almost by definition, these factors will vary among individuals, which also helps to explain the large variations in relapse rates observed within and across individual studies. But even the 34% net effectiveness rate, which is by no means insignificant—given the disturbing impact of psychosis on the individual and his or her social network—does not give an accurate picture of the NLPs' role in helping the schizophrenic function better in society. Until a decade or so ago, most formal evaluations of NLP effectiveness focused on symptom reduction and relapse prevention, not on improved social functioning or integration (Barnes, Milavic, Curson, & Platt, 1983). Symptoms and rehospitalization are relatively easy to measure, but do not reveal how patients really fare overall and over time, in social and vocational spheres. With the advent of "care in the community," researchers have had to broaden outcome measures to include social functioning and quality of life (Diamond, 1985). Yet, according to Meltzer (1992), "There are no studies that demonstrate the outcome of neuroleptic treatment in schizophrenia using all these criteria" (p. 516).

A search of articles published between 1989 and 1993 with the keyword "quality of life" located over 1,200 studies, only three of which dealt with NLPs (see D. Cohen, 1994b). These and earlier studies confirmed the conclusion by Diamond (1985): Although NLPs show some ability to prevent relapse in schizophrenia, they have no direct positive effect on social functioning. Whether on NLPs or on placebo, patients who do *not* relapse have very similar social functioning. In addition, NLP doses (and medication regimen) typically used in the 1980s exerted a negative impact on

social integration (D. Cohen, 1989; Hogarty et al., 1988; Kreisman et al., 1988). In all likelihood, this negative impact results from NLPs' tendency to produce or accentuate social withdrawal or negative symptoms and to interfere with learning and with the ability to apply skills learned during the medicated state to nonmedicated states (Brenner et al., 1994; Lehmann, 1979; Lidz, 1993).

The lack of interest in seriously evaluating medicated patients' quality of life was noted by Awad and Hogan (1994). They attributed this to disagreement on a definition of quality of life, lack of a conceptual model for quality of life on NLPs, and scarcity of reliable and valid measures for the concept, though dozens of sophisticated rating scales exist, able to incorporate quantitative and qualitative evaluations of numerous objective and subjective dimensions. Awad and Hogan nevertheless point to what appears as the key explanation: "... uncritical rejection by clinicians of reports from their schizophrenic patients regarding their feelings about medication.... As psychiatry and psychiatric research has become markedly preoccupied with the 'objective,' a gradual disregard of the subjective dimension of our patients' experiences has followed" (p. 31). This disregard for schizophrenic patients' accounts of their subjective experience is based on the notion that these accounts are unreliable since patients suffer from disturbed thinking and communication. This notion, however, receives no support from the few studies that have attempted to validate subjective impressions of patients with other key informants such as relatives, friends, and clinicians (see, e.g., Epstein, Hall, Tognetti, Son, & Conant, 1989; Kreisman et al., 1988).

Closely related to the issue of quality of life on NLPs is that of negative subjective responses to NLPs. Despite evidence linking the emergence of such responses with poor treatment outcome several weeks and months later (see review by Awad & Hogan, 1994), this area of research, with rare exceptions, has been systematically avoided in the contemporary literature. Patients' negative subjective reactions to NLPs, especially at the initiation of treatment, are one of the most observable aspects of the NLP clinical experience. Scientific neglect of this ubiquitous NLP treatment feature, as well as of an intuitively and objectively important factor bearing on NLP effectiveness, parallels the adoption of clinical strategies aiming to ensure strict compliance with NLP treatment to decrease risk of relapse. Researchers and clinicians may be missing the point entirely for large subgroups of patients.

A meta-analysis of 368 schizophrenia outcome studies from 1895 to 1992 by Hegarty et al. (1994) reveals the relatively limited impact of NLPs as it highlights researcher bias in data analysis. In this study, cohorts from the first two decades of NLP use do show greater improvement (clinical or social) than cohorts from previous decades, especially

the 1910s and 1920s. However, even in cohorts diagnosed with stricter Kraepelinian criteria (associated with lower improvement rates throughout the century), the differences between NLP treatment and convulsive treatments (electroshock, insulin coma, metrazol coma) are not impressive: 31% improvement rate for the former, 27% for the latter, compared with a 22.5% improvement rate for "nonspecific" treatments, defined as "placebo trials, psychotherapy, hydrotherapy, fever therapy, and nonneurological surgery" (p. 1411). When all cohorts are considered, improvement rates for NLP and convulsive treatments are also very similar: 46% and 42%, respectively. Nevertheless, the authors *exclude* convulsive treatment from their multiple regression model to establish predictors of improvement. Of note, improvement declined after the 1970s, reaching the rate of 36% in the 20 NLP outcome studies published since 1986, "a level that is statistically indistinguishable from that found in the first half of the century" (p. 1412). Attempting to salvage the reputation of NLPs, Hegarty et al. conclude their review with this sentence: "In addition to an effect of broad versus narrow diagnosis, the results of this study support a favorable impact of modern treatment, *particularly the use of neuroleptic agents* [italics added]" (1994, p. 1415). Had the researchers not omitted convulsive therapy from the independent variables in the regression equation, the conclusion would be unsupportable. That such an incomprehensible—or ingenious—strategy in data analysis is allowed to pass through the review process of one of the most prestigious psychiatric journals indicates the strikingly prodrug bias in the field today. Furthermore, since the authors define "modern treatment" as NLP *and* convulsive therapies, one is led, again, to ponder precisely what was considered so radically innovative about NLPs when these agents were first evaluated in contexts where the use of convulsive therapies was also widespread.

The results of an unusual study raise other questions concerning the effectiveness of NLPs. Keck et al. (1989) tried to define the onset and time course of antipsychotic effects of NLPs. Out of more than 1,300 published studies, they excluded open trials, studies of chronically psychotic patients, and studies not using a placebo or non-NLP sedative as a control. Astonishingly, this left only five reports. In the three studies of NLP versus placebo, and the two of NLP versus 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)

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)

To summarize the preceding reports on NLPs:

- The ability of NLPs to reduce "relapse" in schizophrenia affects only one in three medicated patients.
- Chronic NLP use depresses social functioning.
- Researchers have systematically avoided studying the role played by patients' subjective responses to NLPs.
- The overall usefulness of NLPs in the treatment of schizophrenia—conceived as a broad, episodic impairment of various social-interpersonal-cognitive abilities—is far from established.

"Nonresponse" to Neuroleptic Treatment

Since the 1989 introduction in North America of clozapine, a drug marketed specifically for "neuroleptic nonresponders," much discussion has focused on this particular group of schizophrenic patients. In 1990, the APA Press published *The Neuroleptic Nonresponsive Patient* (Angrist & Schulz, 1990), perhaps the first book on the subject in nearly 40 years of NLP use. Despite the limited effectiveness of NLPs, previous discussions of NLP nonresponse were rare. The renewed interest in the issue, according to Johns et al. (1990), results from "increasing pressure to shorten the length of hospital stays" (p. 53).

"Response" to NLPs and "effectiveness" of NLPs may be linked conceptually and empirically, but the latter notion typically refers to NLPs' ability to delay relapse, whereas the former refers to NLPs' ability to bring psychotic symptoms under control within a few weeks' time. According to Karon (1989), both "common clinical experience" and "the usual inference from placebo trials" suggest "that medication is useful in the short run in improving immediate clinical status for most schizophrenic patients" (p. 108). Recently, though, some reports estimate a 25% nonresponse rate (e.g., Liberman et al., 1994) and informed observers have suspected that the rate is much higher (Easton & Link, 1986/1987).

What is the rate of nonresponse to NLP treatment for acute episodes of schizophrenia or psychotic symptoms? One answer is found in the results

of a study conducted by Johns et al. (1990). The researchers first administered a "standard dose" of 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 researchers, "review of an earlier pilot study undertaken with 31 schizophrenic inpatients at [their] institution revealed an almost identical response rate (35%) to the same treatment condition" (p. 62). The authors summarize their findings as follows:

> The most striking feature of these preliminary data is the poor response of . . . patients to a standard course of treatment with neuroleptics. 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)

Because of the small sample size, the authors termed their findings "speculative at best" (p. 63). However, 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 et al., 1993). Of the 115 patients who completed the first 4-week phase of the study, 68% were rated as nonresponders. Of the latter who went on to randomized treatment (lower dose, higher dose, or other NLP), "only 4 of 47 subjects (9%) subsequently responded" (p. 309). Despite their surprise with the 63% nonresponse rate in 1990, the authors characterize the 68% nonresponse rate in 1993 as "consistent with a range in previous reports" (p. 310). No data are given on the 41 subjects who did not complete the study; it is not known if they too might be rated as nonresponders and further deflate the dismal response rate.

Systematic studies focusing on nonresponse are scarce, making it difficult to assess how often this occurs in typical practice. Yet, despite NLPs' unique capacities to diminish spontaneous movement or excitation (Clinton, Sterner, Stelmachers, & Ruiz, 1987; Ellison & Pfaelzer, 1995), one senses that nonresponse is quite common. Meltzer's (1992) review of treatment strategies for NLP nonresponders estimates that up to 45% of patients do not respond to NLPs or develop such severe drug-induced behavioral toxicity that treatment cannot be continued after a few weeks. Collins, Hogan, and Awad (1992) rated 50% of all schizophrenic patients hospitalized for more than 6 months in Ontario's largest psychiatric hospital as nonresponders (these patients were nevertheless maintained on daily NLP doses as high as acute patients).

Another indication of high rates of NLP nonresponse—or response so evaluated in current contexts of shorter hospitalization—may be found in rates of polypharmacy with central nervous system (CNS) depressants. Baldessarini et al. (1995) examined pharmacy records of all cases of inpatients treated with a NLP in mid-1993 at their hospital and compared them with a sample of similar cases from 1989. In the interval, length of hospitalization for these patients had decreased markedly, from an average of 73.1 days to 18.5 days. There was no increase in daily NLP dose, but the use of adjunctive anticonvulsants had doubled to 84% of patients in 1993. A "potent benzodiazepine" was prescribed to 81% of patients (unchanged from 1989), lithium was given to 70% (increased from 50% in 1989). Overall, 84% of patients on NLPs received another CNS depressant, 45% two or more (no figures were given for anticholinergic drugs). Separating from this chemical soup the specific impact of NLPs on patients' outcomes may be an impossible task.

Neuroleptic Withdrawal

Faced with NLPs' limited effectiveness and substantial handicaps (see following section), researchers have begun to study the impact of withdrawing the drugs from medicated patients. The issue of NLP withdrawal drew national attention following an article in the *New York Times* (Hilts, 1994) reporting on official blame leveled at University of California researchers for failing to get "proper consent" from schizophrenic patients "in an experiment in which they were taken off their medication and allowed to suffer severe relapses" (p. A1). The researchers were aiming to find out "if some schizophrenics might do better without medication" (p. B10). Although the subjects signed documents stating that they understood the consequences of withdrawal, the severity of some reactions—one subject committed suicide, another threatened to kill his parents—angered patients' families. Many reasons exist to withdraw NLPs from "responding" or "nonresponding" patients under well-monitored conditions. However, there is little psychiatric tradition in initiating and supervising *patient-centered* drug withdrawal to minimize predictable withdrawal reactions.

Support for the foregoing assertion—and further glimpses into the confusion surrounding researchers' judgment of NLP effectiveness—is found in data from the first systematic review of the literature on NLP withdrawal in schizophrenic patients (Gilbert, Harris, McAdams, & Jeste, 1995). Gilbert et al. located 66 English and foreign-language publications (1958 to 1993, involving over 4,000 patients) reporting new data on NLP withdrawal in a minimum of 10 subjects with a diagnosis of schizophrenia or schizoaffective disorder. They found the overall relapse rate of withdrawn patients to be 46.6% for a mean length of follow-up of 7 months. In 29 studies, NLP

withdrawal groups were matched to NLP maintenance groups: after a mean follow-up of 10 months, relapse rate was 53.2% in the former and 15.6% in the latter. This obvious and significant difference, highlighted in the review's text and abstract, nevertheless vanishes under a closer look. Unless a patient is the victim of acute drug-induced toxicity, there exist few good reasons to withdraw a psychotropic drug abruptly. Yet, in 42 of 60 studies (70%) where information about the length of NLP taper was given, NLP treatment "was withdrawn acutely over 1 day" (1995, p. 175).

In their published commentary on this review, Baldessarini and Viguera (1995) re-analyzed the data in 46 studies (33 with abrupt discontinuation—less than two weeks, usually one day—and 13 involving longer discontinuation). They found that "the proportion of patients relapsing per month was threefold greater after abrupt discontinuation of treatment [14.5% vs. 5.3%, $p = .008$]" (p. 191). Surprisingly, Gilbert et al. (1995) report only NLP withdrawal itself and length of follow-up to be significantly associated with the relapse rates. Nevertheless, as Baldessarini and Viguera show, it appears that *gradual* NLP taper might almost erase any differences in relapse rates between withdrawal and maintenance groups.

In their own reply commentary, Jeste, Gilbert, McAdams, and Harris (1995) acknowledge, "Baldessarini and Viguera make an excellent point regarding the relapse rate being three times greater following abrupt withdrawal compared with gradual discontinuation" (p. 211), yet they remain silent on any implications for their results. Here are the implications: *Gradual NLP withdrawal is associated with the same relapse rate as continued NLP treatment.* At the very least, one must endorse Gilbert et al.'s conclusion, which again highlights the little progress made these past four decades in the wise use of NLPs: "There is a critical need . . . to identify patients who do not need long-term neuroleptic maintenance therapy and to optimize strategies for neuroleptic taper that minimize the danger of relapse" (1995, p. 186).

Baldessarini and Viguera's (1995) reanalysis of the Gilbert et al. (1995) data raise other intriguing questions about the extent and nature of NLP iatrogenesis. They show the risk of relapse appears nonlinearly distributed over time, with most of the excess risk after stopping treatment arising early, within the first three months. Baldessarini and Viguera cite almost identical findings from studies of lithium withdrawal in bipolar patients. They suggest, "The state following the interruption of maintenance treatment may not be clinically or psychobiologically identical to that reflected in the natural history of the untreated illness" (p. 190). They propose the existence of an "iatrogenic-pharmacologic stress effect" operating after drug withdrawal, "particularly abrupt interruption." They conclude, "An excess of relapse following *rapid* drug withdrawal may inflate drug vs. no-drug comparisons . . ." (p. 191, italics added).

Many of the studies in the Gilbert et al. (1995) review were probably not designed to study withdrawal; thus withdrawal conditions may not have been carefully planned. Yet, despite its obviously confounding effects, *abrupt* withdrawal is used by van Kammen et al. (1995) to test behavioral and biochemical indicators of schizophrenia relapse. Van Kammen's team is described by Zubin, Steinhauer, and Condray (1992) as using "one of the most closely controlled approaches to studying relapse after withdrawal of medication" (p. 15). In this study of 88 men with a diagnosis of chronic schizophrenia of several years' duration and maintained on HPL, "identical-looking placebo capsules replaced the haloperidol capsules overnight . . ." (van Kammen et al., 1995, p. 674). After six weeks, 60% of patients were classified as relapsing, a rate van Kammen et al. suggest appears "higher than those usually reported" (p. 676). The investigators tested three regression models to predict relapse, but there is no telling how the various independent variables might differ if NLP withdrawal were more gradual. It is reasonable to expect that chemical ratings of neurotransmitter levels and behavioral ratings of psychosis, depression, and anxiety would vary depending on the speed of NLP withdrawal. The researchers went to considerable trouble to collect their data (for example, using lumbar punctures to obtain cerebrospinal fluid from subjects). Their article appears five months after the Gilbert et al. (1995) review of NLP withdrawal studies and the commentary by Baldessarini and Viguera (1995), in the same journal, but nowhere do van Kammen et al. discuss the possible impact on relapse rates and relapse architecture of abrupt NLP withdrawal.

Liberman et al. (1994) describe careful NLP withdrawal, with consequent positive results. Thirteen "treatment-refractory schizophrenic patients" receiving over 50 mg/day of HPL and continually hospitalized for a mean of five years had their NLP dose reduced every 5 weeks by 15 mg/day, as long as the patient was rated unchanged or improved. If the patient was rated slightly worse, the dose was held steady for another 5 weeks, and if rated much worse, the dose was increased to the previous increment. After 5 weeks at their "optimal" dose, the patients received "individualized behavioral analysis and therapy" for target problems such as agitation, assaultiveness, incoherence. Eleven of 13 patients tolerated a mean NLP dose reduction of 88% (most patients still received a benzodiazepine). This "produced improvements in positive symptoms, depression, anxiety, and side effects, and the addition of intensive behavior therapy yielded improvements in functional behavioral and negative symptoms" (p. 758). For 20 weeks, one patient was "remarkably improved at a dose of 0 mg" (p. 757). For 9 patients, the clinical status reached on the "optimal" dose was sustained for a minimum of 1 year of follow-up. Caldwell (1994) provides illuminating case studies of two "extraordinarily

violent" individuals in maximum security hospital units who showed dramatic improvements following drug discontinuation and the application of a "social constructionist" treatment approach. Caldwell pointedly recognizes, "Within the conventional thinking of the mental health field, such so-called miracle cures are simply not believable" (1994, p. 600).

PSYCHOSOCIAL ALTERNATIVES TO NEUROLEPTIC TREATMENT

Several studies comparing psychotherapeutic treatment of schizophrenic patients with NLP drug treatment have been published. The most careful and detailed review of the six major American controlled studies (carried out from 1959 to 1981) was done by Karon (1989). He noted at the outset the prevailing opinion by the end of the 1960s, to the effect that treatment of schizophrenia without medication was unjustifiable. During the 1970s, a few studies modified this opinion to suggest that social treatment improved patients' quality of life and clinical outcome and should be combined with maintenance drug therapy. This opinion, with slight modification and refinement of the psychosocial interventions such that these are seen as important but insufficient ingredients in a comprehensive treatment program, prevails today. For example, in one study (Kleinman, Schacter, Jeffries, & Goldhamer, 1993) the written information on risks and benefits of NLP medication given patients to obtain their informed consent included the statement, "Psychotherapy and social therapy are other forms of treatment used to help patients with schizophrenia, but neither is as effective as neuroleptic medication in preventing relapse" (*Risks and benefits*, no date). This opinion, however, cannot be supported by the available evidence.

Karon (1989) discussed several problems explaining the lack of positive results for psychotherapy found in some of the controlled studies: (a) using unwilling, uninterested, or inexperienced therapists and supervisors, (b) using therapists unfamiliar with patients from lower socioeconomic classes or nonwhite ethnic groups, (c) examining patients on the day of termination of psychotherapy, discharge, and other irregular intervals, (d) not measuring thought disorder carefully, (e) taking ward behavior, not real-world functioning, as a key outcome measure, (f) not following patients in the long-term, or (g) all of the preceding. Despite these strategies, most studies reviewed showed psychotherapy to be at least as effective as NLPs.

The Soteria studies (Matthews, Roper, Mosher, & Menn, 1979; Mosher & Menn, 1978) were mentioned but not reviewed by Karon. These studies, conducted in San Jose, California, between 1971 and 1983, established conclusively that an intensive interpersonal intervention with newly diagnosed schizophrenic patients within a "therapeutic community" context—and staffed by nonmedical, nonprofessional personnel—could

substantially reduce the use of NLPs. Treatment outcome was predominantly positive for approximately 200 acute schizophrenic patients maintained on very low dosage or no NLPs. After 6 weeks, no significant differences in psychopathology levels were observed between 28 index patients treated without drugs at Soteria and 11 hospitalized control patients receiving an average daily dose of 700 mg of chlorpromazine equivalent. At 2-year follow-up, however, the Soteria patients had better levels of social adjustment and occupation, had experienced their psychosis in a less distressing manner, and incurred lower treatment costs. These findings were not subject to systematic replication until the establishment of Soteria Berne in Switzerland in 1984. The treatment program in the latter project, run in a 12-room house accommodating six to eight patients and two staff, was quite similar to that used in the original Soteria, except for a greater reliance on low-dose, targeted medication as well as the systematic use of medical personnel.

Ciompi et al. (1992) reported data on 51 patients treated for at least 10 days and discharged from Soteria Berne between 1984 and 1990, including outcome comparisons over a 2-year period between the first 14 index and 14 matched control patients (hospitalized in four different psychiatric clinics and hospitals). Twenty (39%) of the 51 Soteria received no NLPs during their entire stay, and the rest received "low" doses (about 170 mg/day of chlorpromazine equivalent) for approximately two-thirds of their stay. In 61% of the index cases, the immediate global outcome was rated as "good" or "fairly good," and in 35% as "rather poor" or "poor." Patients receiving no medication demonstrated significantly better clinical results. Matched-pair comparisons were made by matching index and control patients with respect to age, sex, and the two most relevant predictors of outcome, premorbid social adjustment and prevailing positive or negative symptoms. No significant differences were found in seven out of a total of nine outcome and progression variables (including psychopathology, housing arrangements, job situation, social autonomy, and relapse rate). The only significant differences found were for mean daily NLP dose and total cumulative NLP dose. However, treatment costs were significantly higher for the Soteria patients, probably because of the long postdischarge, rehabilitation phase of the Soteria program. While not definitive, these findings confirm those of Mosher and Menn (1978) and Matthews et al. (1979), strongly suggesting that important subgroups of newly diagnosed schizophrenic patients may be helped with no or little use of NLPs.

NEUROLEPTIC-INDUCED BEHAVIORAL TOXICITY

Neuroleptics' near-sacred reputation as "antipsychotics" is only equaled by their record as one of the most behaviorally toxic classes of psychotropic

drugs. In two studies including 2,700 NLP-treated patients (Dencker, Ahlfors, Bech, Elgen, & Lingjaerde, 1986; Segal et al., 1992), patients themselves most frequently report dry mouth, loss of sex drive, agitation, weight gain or loss, sleepiness, diarrhea or constipation, depression or lethargy, vertigo, and general physical weakness. The intensity of the effect matters probably more than its simple occurrence but we lack knowledge on the impact of subtle but persistent drug-induced dysfunction.

The most widely acknowledged yet least scientifically studied effects of NLPs are the lethargy and negative symptoms they induce in patients. Recent descriptions of these effects are given by Wallace (1994), who summarized topics discussed by thousands of callers to SANELINE, a telephone helpline for people diagnosed or coping with severe mental disorders. After queries for actual psychological or medical help, the second most common reason for calling SANELINE is worries about medication.

> What we have found is that most people with schizophrenia dislike taking the drugs they are being prescribed. . . . [T]he negative parts [of the side effects] are perceived as quite often worse than the illness itself. . . . [I]n the anonymity of phone calls to SANELINE, even the most deluded person is often extraordinarily articulate and lucid on the subject of their medication. . . . "When I take my medication, I feel as though I am walking with lead in my shoes" one young man told me on the telephone. Another told the volunteer who took his call "I feel emptied out, devoid of ideas." Another young man sent us a poem in which he compares the effects of the drugs with drowning—"I was always under the water gasping for air and sunshine," he writes. . . . 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)

Acute manifestations of EPS are occasionally reported present in 90% of NLP-treated patients (Casey, 1989, 1991). It is beyond the scope of this critical review to describe EPS in detail (see Kane & Lieberman, 1992a; Keshavan & Kennedy, 1992). Nor will there be a discussion of neuroleptic malignant syndrome, an explosive toxic reaction affecting 0.5% to 2% of NLP users, with a reported fatality rate of 5% to 30% (Addonizio, Susman, & Roth, 1987). Topics touched on here will include some problems EPS pose for patients and clinicians, professional-clinical reactions to EPS, prevention of tardive dyskinesia, and controversies surrounding ominous long-term NLP effects such as tardive psychosis and tardive dementia. The backdrop for this discussion is the commonly held notion that the advantages of NLP treatment outweigh its drawbacks.

Reifying "Side Effects": Obstacle to Realistic Assessment of Neuroleptic Effects

The psychiatric literature distinguishes between "main" and "side" effects of psychotropic drugs. The first are "therapeutic" effects, the second are "toxic" (or "adverse") effects. What actually distinguishes a main effect from a side effect is not the action of the chemical substance but rather the *intent* of the prescriber: a "side" effect may be just as frequent as, or more common than, a "main" effect (see Dewan & Koss, 1989, p. 216), but it is unwanted. However, for a given individual (patient or clinician) at a given time, one drug effect may be desirable and another undesirable, or both sought simultaneously. At what point does NLP-induced sedation and indifference (valued during the acute psychotic episode) become "akinetic depression" or, later, "NLP-induced deficit syndrome" (condemned as a major chronic treatment complication)? When does "effective reduction of psychomotor excitation" become "NLP-induced parkinsonism"? When does "reducing the flow of unfiltered external stimuli" become "intense distress with one's discomfort" (in severe akathisia)? Individual patient differences aside, the drug's range of actions does not commonly vary, but these will be categorized according to the requirements of the social-interpersonal-clinical situation. If this analysis has merit, the distinction between "therapeutic" and "adverse" effects has been reified by clinicians and researchers, operating in a zeitgeist of propsychotropic drug bias.[6]

As a class of psychotropics originally named because their neurological toxicity coincided with the sought-after goals of treatment, NLPs exemplify the preceding point. Furthermore, the clinical reality of inextricable link between "therapeutic" and "toxic" has probable biochemical parallels. In 1963, Carlsson (1975) suggested that NLPs blocked striatal dopaminergic (DA) receptors. It was later shown that an NLP's ability to occupy 65% to 80% of D_2 receptor sites correlated with its "antipsychotic potency." The DA hypothesis of NLP action—not fully satisfactory to explain most observations but still dominant (see Kahn & Davis, 1995)—thus attributes NLPs' "therapeutic" effects to D_2 receptor blocking. Yet that is precisely the same mechanism invoked to account for EPS and, with alterations in the DA and other neurotransmitter systems after prolonged blockade, for TD. The ongoing discovery since the 1970s of several families of DA receptors and the observation that NLPs such as clozapine have lesser affinity for D_2 receptor blockade and lower frequency of EPS, led to the current belief that particular biochemical actions (i.e., blockade of D_3 and D_4 receptors and/or receptors from other neurotransmitter systems) can produce "main" effects

[6] Of course, similar considerations apply to other types of drugs (see Montagne, 1988).

without producing "side" effects. Based on what we know about the brain and its nearly infinite yet integrated complexity, such a belief may be illusory, reminding one of the futile search for nearly 60 years now, of "anxyolitic" molecules not inducing dependence or sedation.

Do NLPs produce distinct desired effects (antipsychotic) *in addition* to distinct undesired effects (adverse) or do they produce a *global neurological syndrome* that can be evaluated in some contexts and over time as partially or fully beneficial? In the case of illicit psychotropics (which many users actually report *liking*), researchers have no difficulty conceptualizing desired effects as in fact part of a spectrum of psychological and neurological toxicity. In the case of NLPs (which most users actually report *disliking*), there is strong resistance to this idea. This suggests that a naive realism pervades psychopharmacological research.

NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL SYMPTOMS (EPS)

The main types of EPS include parkinsonism, dystonia, akathisia, and dyskinesia. In a clinical context showing enthusiasm toward NLPs, and without the standardized rating scales developed the following decade, Ayd (1961) observed a global incidence of 39% among nearly 4,000 NLP-treated-patients. Twenty years later, Ayd (1983) estimated a 61.9% incidence.

Among EPS' most disturbing characteristics is that they resemble typical psychiatric symptoms (i.e., they add significantly to any preexisting emotional-mental problems and may not be recognized as drug-induced); they may remain resistant to chemical treatment; and they may become irreversible, even after complete cessation of NLPs. Each syndrome may occur alone, as a distinct entity, or concomitantly with other drug-induced syndromes. Each syndrome may appear any time during NLP treatment. Each is traditionally characterized as "acute" when it arises early in the course of treatment and "tardive" when it appears after months or years, but there exists no clear phenomenological distinction between the two forms. On a pharmacological level, however, early-appearing EPS are *always* lessened by reducing the NLP dose and sometimes by adding an antiparkinsonian (anticholinergic) drug, which partially and temporarily restores the dopamine-acetylcholine equilibrium upset by D_2 receptor blockade. Tardive EPS, on the other hand, are usually unaffected or worsened by a dose reduction. Similarly, EPS are reversible at the beginning, but may become irreversible later. There is no way to know this in advance—only discontinuation of NLPs will tell: Cases that resolve will be termed "reversible" and those that persist, "irreversible." At best, a tardive syndrome will show decrease of the symptoms over time and may be slightly relieved by symptomatic treatment.

Parkinsonism and Akinetic Depression

The first symptoms of NLP-induced parkinsonism, also called pseudoparkinsonism, are identical to those of idiopathic Parkinson's disease: reduced facial expression, reduced arm swing, general muscular rigidity, monotonous speech. This is often referred to as akinesia or hypokinesia. Postural instability, tremor of the extremities, and hypersalivation appear sometimes. As noted, the reduced motor and psychic spontaneity may be indistinguishable from negative or deficit signs of schizophrenia or from a postpsychotic depression: they are frequently unrecognized (Van Putten & Marder, 1987, p. 15).

Van Putten and May (1978) found that 30% of 94 chronic schizophrenic patients showed pure akinesia, 17% had akinesia and other EPS, 19% had EPS without akinesia, while 34% had no EPS. Parkinsonism typically appears between a few hours and 20 days after the start of NLP treatment and tends to disappear gradually after a few months (Herrington & Lader, 1981). In a small percentage of cases, it will reappear, persist, and worsen, months after the cessation of NLPs (Melamed, Achiron, Shapira, & Davidovicz, 1991).

Rifkin, Quitkin, and Klein (1975) described a 22-year-old NLP-treated man, whose anticholinergic drug was switched to placebo following his enrollment in a clinical study. Two weeks later, the man became quite depressed and suicidal as a result of his being completely unable to sustain conversations at social events. An hour after reinstitution of the anticholinergic, the symptoms were greatly reduced and disappeared in 24 hours. However, the parkinsonism persisted in the form of a rigid gait. Because of parkinsonism's frequency and resemblance to negative symptoms, such examples of complex NLP emotional-behavioral toxicity are doubtless more frequent than the number of published case studies would suggest.

Dystonias

Dystonias are strange, uncoordinated movements produced by sustained muscular spasms, mostly affecting the head and neck, occasionally the extremities and the trunk. Forced opening of the mouth, protrusion and distortion of the tongue result in speech, swallowing, and breathing difficulties (laryngeal dystonia). The individual may show an empty, fixed stare, followed by vertical or lateral movements of the eyes (oculogyric crises). Or, the eyes may be forced tightly shut (blepharospasm). Possibly the most extensive descriptions of dystonia and tardive dystonia are by Burke et al. (1982) and Burke and Kang (1988).

Acute dystonias generally appear between 1 hour and 5 days after the start of NLPs, a dose increase or a sudden NLP change. Dewan and Koss (1989) report prevalences averaging 1% to 10%. Because dystonias often

occur suddenly, are painful and bizarre, they frighten patients and families. This must be appreciated in light of the fact that younger patients, especially men, seem more predisposed (Klein, Gittelman, Quitkin, & Rifkin, 1980). NLPs such as haloperidol, molindone, and the piperazines are more likely to produce dystonic reactions than other drugs (Bezchlibnyk-Butler & Jeffries, 1996).

Contrary to the tardive dyskinesias, where older patients and women are at higher risk, young and old patients are equally at risk of developing tardive dystonia, with an estimated prevalence of 1% to 5%. Yadalam, Korn, and Simpson (1990) described four such cases, in three of which the abnormal movements interfered "with all daily activities" (p. 17).

AKATHISIA

Recognized today as the most frequent (5% to 76% incidence) and distressing EPS, akathisia was relatively ignored by researchers until recently (Sachdev & Loneragan, 1991). This may be partly because the problem is often subjective, described differently by patients: inability to sit still, a sense of gloom and anxiety originating in the abdomen, restless legs, and so forth (Lavin & Rifkin, 1992). In "mild" cases, the individual may show no visible movement (especially if there is a co-occurring akinesia) but nevertheless feel significant psychic agitation or muscular tension. When visible, the motor agitation typically takes the form of shifting weight from foot to foot or walking on the spot, inability to keep legs still, shifting of body position while sitting (Sachdev & Kruk, 1994). Akathisia usually appears within hours or days of the start of NLPs and is often mistaken for psychotic agitation; this may result in a NLP dose increase, which worsens the akathisia (Lavin & Rifkin, 1991). In one study (Hermesh, Shalev, & Munetz, 1985), akathisia was reported to contribute to 3.4% of emergency hospital admissions. In extreme cases, it has led to suicide and homicide (Van Putten & Marder, 1987).

Akathisia is frequently accompanied by a dysphoric mental state, described by some normal subjects as a "paralysis of will" (Belmaker & Wald, 1977). A medical student who received 1 mg of HPL described the sensation of an external force forcing him to move (Kendler, 1976). Vaughan, Oquendo, and Horwath (1991) described the case of a 34-year-old man on fluphenazine who developed a severe akathisia and attributed his agitation to an external force, described by Vaughan et al. as a "psychotic delusion." Manos, Gkiouzepas, and Logothetis (1981) described patients who experienced psychotic flare-ups, making statements such as "A woman tried to strangle me last night," "I burn inside," and "A pair of pliers squeezed my body and throat." However, the authors stressed that the symptoms were subjective accounts of objective

manifestations of disturbing EPS. Commenting on these cases, Lavin and Rifkin (1991) believe, "It is likely that [they] occur more frequently than is usually recognized" (p. 1615).

Tardive akathisia—which resists any treatment and persists despite NLP discontinuation—represents a particularly troubling problem. Its prevalence has been estimated at 18% of patients referred to a TD evaluation clinic (R. J. Davis & Cummings, 1988), and 14% among 180 intellectually handicapped individuals treated with NLPs (Gualtieri, 1990). Gualtieri (1993) illustrates well a dilemma posed by chronic NLP use: after attempting and failing to discontinue NLPs (because of the acute behavioral and motor flare-ups) in a group of intellectually handicapped individuals with tardive akathisia, he concludes that these unfortunates are condemned to remain on the drugs because of NLP-induced toxicity.

Tardive Dyskinesia

Bezchlibnyk-Butler and Jeffries (1996) estimate the risk of TD (in adult patients) as "38% after 5 yrs, 56% after 10 yrs" (p. 45). Most cases are of "mild" intensity. An undetermined proportion (5%–10%?) are very severe and incapacitating. Occasionally, some authors muse about the impact of factoring TD into the cost-benefit ratio of prolonged NLP treatment, but this has never been done seriously in the mainstream literature (but see Dewan & Koss, 1989). As will be discussed, significant resistance still exists today about its prevention.

The TD syndrome (which includes tardive dystonia and tardive akathisia) is a complex disorder that includes up to 25 different abnormal movements (Singh & Simpson, 1988). Movements and grimaces of mouth, tongue and lips predominate in about 80% of patients (Kane & Lieberman, 1992b). Tics and mannerisms are sometimes confounded with TD, especially among intellectually handicapped persons, and abnormal movements resembling TD were described in psychotic patients well before NLPs were introduced. Nevertheless, since the first reported cases, the prevalence of TD has grown significantly. In 1981, Jeste and Wyatt estimated a 13% prevalence rate, which had increased to 24% a decade later (Yassa & Jeste, 1992).

A recent study with 2,250 subjects shows how rates vary depending on the populations studied: 36% of chronic, hospitalized patients had signs of TD; among less frequently hospitalized patients, the rate was 13%; among those never exposed to NLPs, including elderly persons, the rate of spontaneous or senile dyskinesia varied between 0% and 2% (Woerner et al., 1991). Lower rates among chronically hospitalized patients in Italy and in China (see Yassa & Jeste, 1992) suggest that higher NLP doses used in North America help explain the scope of the problem here. There are

remarkably few actual *number* estimates of TD victims. Dewan and Koss (1989) provide such an estimate, although based on extrapolations from a 1983 study of outpatient NLP use in the Unites States. Their best-case and worst-case scenarios result in the astounding range of 90,000 to 625,000 people who suffer *irreversible* TD in a given *year*.

In up to 85% of elderly patients with TD, there is complete unawareness of the movements (Myslobodsky, 1986). This anosognosia is typically found in syndromes of generalized brain dysfunction. Institutionalization, schizophrenia, psychic indifference produced by the NLPs, mental deterioration, and dementia (including NLP-induced tardive dementia), have been invoked, singly or together, as factors explaining it (Bourgeois, 1988).

Aside from NLP exposure, the only unanimously recognized risk factor is advanced age, which also increases the probability of TD persisting. Yassa, Nastase, Camille, and Belzile (1988) found that 41% of patients over 63 years developed TD after only 2 years of NLP treatment. Female gender is also consistently implicated. Individual studies suggest a dozen other factors, including previous EPS, diagnoses of affective disorders, cumulative NLP dose, concomitant use of antiparkinsonians, previous existing brain damage or use of convulsive treatments, frequent NLP holidays. All NLPs commonly used are likely to provoke TD, with fluphenazine sometimes said to pose a higher risk. Hill (1983) denounced the fact that, given ongoing use of NLPs, research priorities have not been directed at ruling out whether any particular NLPs pose higher risk.

After 5 years, in patients in whom NLPs are discontinued, the rate of spontaneous remission of TD ranges from 14% to 40% (Bezchlibnyk-Butler & Jeffreys, 1996; Casey, 1985; DeVeaugh-Geiss, 1988). In patients maintained on NLPs, however, results are less encouraging. Yassa et al. (1984) observed remission after 2 years in 16% of 55 TD patients; DeVeaugh-Geiss (1988) reported no improvement in 17 patients after 1 year; Bergen et al. (1989) reported improvement in only 11% of 101 patients after 5 years; Glazer, Morgenstern, and Doucette (1991) reported that 58% of 192 TD patients followed for 3 to 55 months showed a "chronic and persistent" pattern, the rest an "intermittent" pattern.

The main medical complications of TD include breathing problems (Turnier, Desrosiers, & Chouinard, 1988; Yassa & Lal, 1986), gait and posture problems (Lauterbach, Singh, Simpson, & Morrison, 1990), gastrointestinal dysfunction (Goldberg, Morris, & Lidofsky, 1990), as well as speech problems (Laporta, Archambault, Ross-Chouinard, & Chouinard, 1990). These appear to result directly from the abnormal movements affecting certain muscles. In the elderly, oesophegeal, diaphragm, and respiratory dyskinesia "may be fatal" (Turnier et al., 1988, p. 41).

Cognitive and Psychosocial Complications of Tardive Dyskinesia

Most known motor disorders appear to produce a deterioration of cognitive functions. About 30 studies have assessed the cognitive functioning of patients with TD and have established that, in particular, various memory and nonverbal dysfunctions are associated with TD (H. Cohen & D. Cohen, 1993a, 1993b). The severity of cognitive deficits sometimes correlates positively with the severity of the movements. The main research questions center around determining whether these deficits predate the apparition of TD, result directly from presumed brain lesions caused by NLPs and underlying TD, result from the psychiatric disorder, or develop from an interaction of these or other factors. The primary impediment to answering these questions remains the unwillingness or inability of researchers—given the official view of NLPs as essential or lifesaving—to constitute and follow a sizable control group of unmedicated schizophrenic patients.

Psychosocial complications of TD have been documented, including suicidal thoughts, higher death rate, and vocational problems (Yassa, 1989). Although evidence remains mostly anecdotal, D. Cohen (1994b) noted that only one or two published studies have looked specifically at psychosocial dimensions of TD, and has suggested that TD is a socially stigmatized condition. For example, in the first complete description of TD, by Schöneker in 1957, the author wrote, "The repetitive mouth movements . . . were repugnant to people around [the patient]" (as cited in DeVeaugh-Geiss, 1982, p. 201). For Mosher and Burti (1989), "The dyskinesic is stigmatized by the impossible-to-hide, cosmetic disfigurement of tardive dyskinesia" (p. 3). According to Diamond (1985), "the movements tend to change the appearance of the patient and accentuate social distance" (p. 32). Among 22 patients interviewed by Yassa (1989), 12 complained of embarrassment caused by their abnormal movements and by reactions from people in public places.

Tardive Dementia and Tardive Psychosis

The issue of psychopathological symptoms appearing during prolonged NLP treatment was debated for some years in articles on "tardive dysmentia." Wilson et al. (1983) first proposed the term to describe certain behavioral changes seen in prolonged NLP treatment. These changes showed strong positive correlation with TD and were described as a "behavioral equivalent" of TD: loud voice, loquacity, incoherent speech, euphoria that could rapidly turn into hostility, autistic preoccupations punctuated with hyperactivity and intrusiveness. Like TD, this syndrome would result from

a hyperactivity of the striatal DA system caused by chronic NLP antagonism. Mukherjee (1984) implicated schizophrenia as the cause of this dementia-like syndrome, but Jones (1985) felt that it was an iatrogenic complication of NLPs. In Myslobodsky's (1993) case descriptions, tardive dementia is presented as a behavioral and psychological disorder certainly associated with TD and characterized as "a paradoxical combination of apathy, irritability, and euphoria" (p. 89). Myslobodsky suggests that TD represents "larval dementia."

The concept of "subcortical dementia" (Cummings, 1990) may shed light on that of tardive dementia. The former refers to a slowing of cognitive and motor functions, impaired recall, emotional problems—especially depression and apathy—as well as deficits in so-called executive functions (primarily involving concept formation and the capacity to change mental set). Signs of subcortical dementia are notably visible in diseases of the extrapyramidal system (Parkinson's, Huntington's). Physiological, cognitive, and behavioral parallels between these two diseases and TD suggest that tardive dementia of the NLPs may be a variant of subcortical dementia (Breggin, 1990; Myslobodsky, Tomer, Holden, Kempler, & Sigal, 1985).

Supersensitivity or tardive psychosis has also been associated with chronic NLP treatment. Chouinard and Jones's (1980) diagnostic criteria include appearance after NLP reduction or withdrawal; mostly made up of positive schizophrenic symptoms; concomitant signs of DA supersensitivity, such as TD; association with central nervous system tolerance to NLPs, necessitating increased doses to maintain the antipsychotic effect. NLPs constitute the most effective "treatment" for the disorder, which exists on a severity continuum. The final phase of tardive psychosis is an irreversible, manifest psychosis that continues despite NLP treatment. This ominous entity remains controversial. For example, Chouinard, Annable, and Ross-Chouinard (1986) reported a 27% prevalence of "definite" cases among 224 chronic schizophrenics on NLPs, while Hunt, Singh, & Simpson (1988), only found 12 "probable" cases after a chart review of 256 patients.

The syndromes of tardive dementia and tardive psychosis illustrate the potentially complex and far-reaching nature of NLP effects. As for any drug effect, a good dose of skepticism is required to evaluate their validity. However, given what is known about the action of NLPs on the central nervous system and given their visible effects on mood and behavior, there is ample justification and evidence to entertain the hypothesis that these irreversible syndromes are consequences of NLP treatment. Yet, if previous professional reactions to TD are any indication, one should not expect researchers or policymakers to hastily tackle the prevention or implications of these other tardive NLP iatrogenic syndromes.

Professional Resistance to Preventing Neuroleptic Iatrogenesis

Despite TD's significance as a public health problem, psychiatrists in North America have resisted taking effective steps to deal with it. A gleaning of the relevant literature reveals three types of resistance: resistance to informing patients about TD, to changing prescription habits, and to acknowledging the noxious effects of NLPs.

D. Cohen and McCubbin (1990) found evidence of large NLP dose increases in the 1970s and 1980s and of nonrecognition or misdiagnosis of TD in clinical practice (see also Hansen, Brown, Weigel, & Casey, 1992). They saw no indication that the incidence of TD was about to decline. In addition, Wolf and Brown (1988) observed, "Few institutions have adopted the APA guidelines, and in those that have, many professionals try to circumvent them. Even when informed consent about psychiatric treatment is seriously pursued, patients are provided little information about side effects. When side effects are mentioned, tardive dyskinesia is frequently not among those named" (p. 24).

Nearly a decade later, Meltzer (cited in Gerlach & Peacock, 1995, p. 32s) pointedly asked: "How good a job are we really doing in making patients aware, at the onset of treatment with typical neuroleptics, that they are facing a 30% risk of irreversible tardive dyskinesia once it is established that they need prolonged treatment, or that there is an 80% risk over the course of time that they would have significant EPS?" Data from two recent surveys provide a depressing answer. Kennedy and Sanborn (1992) surveyed 520 state or county hospital psychiatrists in 35 American states. Almost half of respondents said they routinely fail to disclose to their patients on NLPs that they run any risk of developing TD. Given the sensitive topic of the survey, we can only speculate how many respondents would not so admit. For their part, Benjamin and Munetz (1994) surveyed directors of 160 Community Mental Health Centers in the United States about their TD screening practices. Only 41% reported having any monitoring system in place to detect the condition. Benjamin and Munetz conclude that their results are due to "the denial of tardive dyskinesia, plus the great fear that making its risk known will drive patients off their needed medication" (p. 346).

Resistance to viewing TD as a frank neurological disorder also appears strong. Although TD's precise physical correlates are still unknown, a syndrome of involuntary movements—especially when it assumes an irreversible form—can *strongly* be considered to have an *organic, structural* substrate. Here is a (moderately) clear expression of this idea (published in a European psychiatric journal): "[all EPS] entail the risk of becoming

irreversible and may thus be an expression of the neuroleptic's ability to produce persisting central nervous system changes" (Gerlach & Peacock, 1995, p. 27s). However, because of NLPs' near-sacred standing in schizophrenia treatment, TD remains conceptualized as being not exactly what it looks like: a progressive, drug-induced brain syndrome with accompanying physical, behavioral, and cognitive complications (H. Cohen & D. Cohen, 1993).

Neuroleptic effects, like those of any other psychotropic, result from an interaction between the drug, the individual, and the context. This helps explain why abnormal movements characteristic of TD may change over time, be exacerbated during periods of stress, attenuated temporarily by efforts of concentration, be less bothersome to chronically institutionalized patients, and so forth. However, despite occasional findings of spontaneous or senile dyskinesia in unmedicated patients, the weight of the historical, epidemiological, and clinical evidence with humans, and of the experimental laboratory evidence with animals, points overwhelmingly in one direction: NLP drugs "cause" TD. Nevertheless, one may still observe that psychiatric researchers exaggerate the importance of any data that cast doubt on the causal connection or seize opportunities to exonerate NLPs and limit their own responsibility in the production of TD. An outstanding example appears in an article by Fenton, Wyatt, and McGlashan (1994). Having found the presence of oral-facial dyskinesias documented in the records of 15 of 100 presumably NLP-naive schizophrenic patients, the authors offer the following advice in an unprecedented conclusion titled "Medicolegal Caution": "Those physicians who find the case for a significant prevalence of spontaneous dyskinesia in schizophrenia compelling may find it prudent to inform patients and families that the progression of *schizophrenia* [italics added] . . . may be accompanied by the emergence of movement disorders" (p. 649). One looks in vain across the medical literature for similar prominently titled cautions advising physicians to inform patients and families of the prevalence of a vastly more compelling case, that of the emergence of movement disorders with the progression of *NLP treatment.*

CONCLUSION

This selective review of the literature suggests that the value of NLPs in the short- and long-term treatment of schizophrenia has been greatly exaggerated. Forty-five years of NLP use and evaluation have not produced a treatment scene suggesting the steady march of scientific or clinical progress. On the contrary, NLP drug treatment varies widely from country to country, decade to decade, even state to state or hospital to hospital.

Unquestionably, NLPs frequently exert a tranquillizing and subduing action on persons episodically manifesting agitated, aggressive, or disturbed behavior. This unique capacity to swiftly dampen patients' emotional reactivity should once and for all be recognized to account for NLPs' impact on acute psychosis. Yet, only a modestly critical look at the evidence on short-term response to NLPs will suggest that this often does not produce an abatement of psychosis. And in the long-run, this outstanding NLP effect probably does little to help persons diagnosed with schizophrenia remain stable enough to be rated as "improved"—whereas it is amply sufficient to produce disabling toxicity.

A probable response to this line of argument is that, despite obvious drawbacks, NLPs remain the most effective of all available alternatives in preventing relapse in schizophrenia. However, existing data on the effectiveness of psychotherapy or intensive interpersonal treatment in structured residential settings contradicts this. Systematic disregard for patients' own accounts of the benefits and disadvantages of NLP treatment also denigrates much scientific justification for continued drug treatment, given patients' near-unanimous dislike for NLPs. Finally, when social and interpersonal functioning are included as important outcome variables, the limitations of NLPs become even more evident and the systematic implementation and evaluation of nondrug treatment alternatives even more pressing.

Despite the extraordinary interest generated by the introduction and now widespread use of "atypical" NLPs, and of published findings of relatively greater efficacy and lesser toxicity, it is too early to tell whether these represent a true step forward or merely another false dawn. It may be that—whatever neurotransmitters may be targeted by a particular compound—rapid or effective control of spontaneous psychomotor activity can only be obtained for a "price" (i.e., behavioral or other toxicity). Any other expectation might be, simply, unrealistic. Furthermore, scientific inquiry and communication do not take place in a vacuum; the majority of individuals who conduct research in psychopharmacology operate within a profoundly prodrug context and have a direct stake in the maintenance of the scientific and clinical status quo. This long-standing positive bias in favor of NLPs is continually highlighted, as when published research findings pointing to blatant deficiencies, disadvantages, or ineffectiveness of NLPs remain unexamined or are simply glossed over, even by the very researchers who generate them.

In the field of psychopharmacology, concerned with drugs specifically designed or prescribed to alter the functioning of the central nervous system, the distinction between main and side effects may be no more than a once-heuristic concept to guide clinical practice. Yet, despite this

ubiquitous conceptual distinction and the development of tools to identify and map numerous undesirable cognitive, emotional, and physical effects of NLPs, their impact has been barely studied in relation to both short- and long-term clinical and social outcome in schizophrenia. Combined with the lack of active interest in actual and potential tardive iatrogenesis from the NLPs—in the form of chronic deficit syndromes—the state of research and practice seems even more unsatisfactory. Huge gaps remain in our knowledge of NLP drugs; partially filling only some of these gaps could profoundly alter the conventional view on the effectiveness of NLPs. The positive consensus about NLPs cannot resist a critical, scientific appraisal.

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