

Delayed-Onset Hypothesis of Antipsychotic Action

A Hypothesis Tested and Rejected

Ofer Agid, MD; Shitij Kapur, MD, PhD, FRCPC; Tamara Arenovich, MSc; Robert B. Zipursky, MD, FRCPC

Context: To understand the mechanism of action of antipsychotic drugs, it is critical to recognize the time course over which these medications take effect. Current models of antipsychotic action presume a “delayed onset” of action.

Objective: To test the delayed-onset hypothesis of antipsychotic action via a meta-analytic study.

Data Sources and Study Selection: Double-masked studies that reported results from active or placebo-controlled trials of antipsychotic response during the first 4 weeks of treatment were selected. These studies were identified by searching MEDLINE, 1996 to 2001; the Cumulative Index to Nursing and Allied Health, 1982 to 2001; EMBASE, 1980 to 2001; the ACP Journal Club; the Cochrane Database of Systematic Reviews; and the Database of Abstracts of Reviews of Effectiveness. Leads from these sources were followed up by manual searches.

Data Synthesis: Forty-two published studies, including 7450 patients and 119 independent response vs time curves, were identified. Reductions in total scores on the Brief Psychiatric Rating Scale and the Positive and Negative Syndrome Scale were 13.8% during week 1, 8.1% during week 2, 4.2% during week 3, and 4.7% during week 4. This pattern of “early-onset” improvement was present even after the estimated effect of placebo treatment was removed and when results were restricted to the psychotic subscales of the scales.

Conclusions: This analysis rejects the commonly held hypothesis that antipsychotic response is delayed. Rather, these findings suggest that the antipsychotic response starts in the first week of treatment and accumulates over time. Furthermore, greater improvement occurs in the first 2 treatment weeks than in the subsequent 2 treatment weeks. Proposed mechanisms of action of antipsychotic drugs need to account for this early-onset antipsychotic effect.

Arch Gen Psychiatry. 2003;60:1228-1235

TREATMENT OF psychotic illness before the 1950s was often difficult and sometimes even dangerous.¹ In 1952, the introduction of chlorpromazine marked the beginning of the modern era of psychiatric pharmacotherapy, eventually leading to the atypical antipsychotic agents available today. Although the efficacy of these medications for the treatment of psychosis is well established, debate continues over their precise mechanism of action.

In the 1960s, Carlsson and Lindqvist² proposed that the effect of antipsychotic medications was due to their effects on the monoaminergic system. In the 1970s, it was reported³⁻⁵ that antipsychotic drugs displace dopamine from its receptor with an affinity that correlates with their clinical potency. As a result of these findings, it has been generally accepted that a central pharmacologic property of antipsychotic drugs is that they act by blocking the effects of

dopamine at D2 receptors.^{3,6} Although a stable level of dopamine blockade is achieved within a few days of starting treatment, substantial improvement may not occur for several weeks. Understanding this apparent delay is a question of fundamental concern to the field.

The notion that there is a substantial lag between antipsychotic drug administration and clinical improvement has had a major effect on the field. The term “delayed onset” of antipsychotic medication effects was coined in the 1970s and is now well established in standard psychiatric textbooks.⁷⁻¹⁰ According to this hypothesis, there is delay of 2 to 3 weeks between the start of medication administration and the onset of specific therapeutic benefits, although dopamine receptor blockade is well established in the first few days. The “depolarization block” hypothesis has been proposed as an explanation for this delay. This hypothesis suggests that repeated administration of antipsychotic

From the Schizophrenia Program (Drs Agid, Kapur, and Zipursky) and the PET Centre (Drs Agid and Kapur), Centre for Addiction and Mental Health, and the Departments of Psychiatry (Drs Agid, Kapur, and Zipursky) and Statistics (Ms Arenovich), University of Toronto, Toronto, Ontario.

agents causes dopaminergic neurons in the brain to undergo inactivation of firing. This inactivation of firing has been proposed as a critical step in mediating antipsychotic response and has been consistently observed in rats after 3 weeks of continuous treatment. It has been suggested that this 3-week period may explain the delay in onset of the therapeutic effect and the neurologic adverse effects of these drugs on patients with schizophrenia.⁹⁻¹⁷ However, the precise time course of clinical improvement seen with antipsychotic drug treatment has never been definitively established.

An important distinction needs to be made between a delayed onset and a delayed realization of full improvement. Although there can be no debate that full therapeutic benefits take several weeks to realize, this by itself does not imply a delay in the onset of action. In almost every area of medical therapeutics, from antibiotics to chemotherapeutic agents, medicines take time to realize their full benefits, thus a delay in full benefits does not by itself imply a delayed onset of action. Because the concept of delayed onset has become widely accepted, we examined whether the available clinical evidence supports such a claim.

The earliest studies of chlorpromazine treatment in the 1950s^{18,19} describe clinical improvement within days of starting treatment. A variety of more recent studies have reported similar findings. Stern et al^{20,21} showed that early response occurs with typical and atypical antipsychotic medications. McDermott et al²² found that 40% of patients with schizophrenia responded to haloperidol therapy between days 8 and 18 of treatment, and Garver²³ described dramatic antipsychotic effects in a group of patients with schizophrenia by the fourth day of antipsychotic drug administration. Several other investigators²⁴⁻²⁸ have reported responses within the first 10 days of drug treatment. Although the interpretation of these studies is limited by their being either anecdotal reports or open, uncontrolled clinical trials, they cause one to question whether the onset of antipsychotic action is actually delayed.

The previous considerations lead to 2 competing hypotheses concerning the onset of action of antipsychotic drugs, either of which would account for the observation that substantial clinical improvement takes weeks to achieve:

- Delayed-Onset Hypothesis: After the drug reaches its therapeutic level, there is a period of “delay” before response begins. This delay has been proposed to be approximately 2 to 3 weeks.
- Early-Onset Hypothesis: The antipsychotic effect starts simultaneously with the drug reaching its therapeutic levels (ie, in the first few days). As with any continuous process, the effect accumulates over time and finally plateaus. In contrast to the delayed-onset hypothesis, there is no notable delay in improvement; on the contrary, there is more improvement in the earlier weeks than in the later weeks.

Graphically, these hypotheses would appear as shown in **Figure 1**. Both hypotheses can explain why it may take several weeks to achieve a substantial level of response. However, they make opposite predictions regarding what happens early in the course of treat-

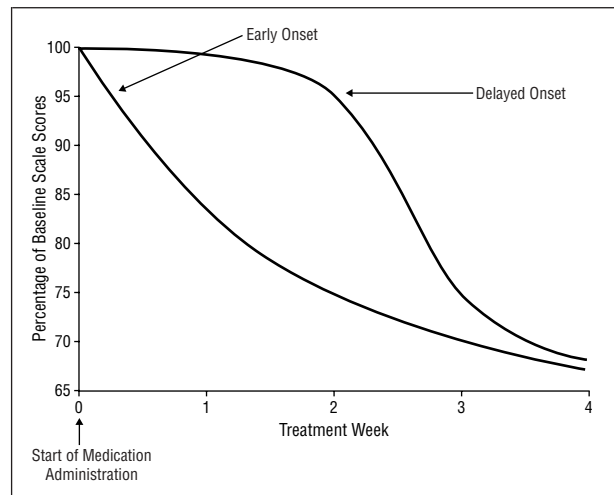


Figure 1. Delayed-onset hypothesis vs early-onset hypothesis.

ment. Distinguishing between these 2 competing models of antipsychotic onset is of significant clinical and theoretical importance, as the 2 different trajectories will lead to different clinical expectations, different clinical trial designs, and different kinds of mechanisms to explain the effects of antipsychotic medications. To determine whether the onset of action of antipsychotic medications is most consistent with the delayed-onset hypothesis or with the early-onset hypothesis, we evaluated existing clinical trial data using a meta-analytic approach.

METHODS

DATA SOURCES

We reviewed the English-language published data from active and placebo-controlled, double-masked studies of antipsychotic treatment in patients with schizophrenia or schizoaffective disorder during the first 4 weeks of antipsychotic drug treatment. Articles for this review were obtained by searching the MEDLINE electronic database, 1996 to 2001; the Cumulative Index to Nursing and Allied Health, 1982 to 2001; EMBASE, 1980 to 2001; and the Evidence-Based Medicine Reviews multifile database (the ACP Journal Club, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effectiveness).

DATA SELECTION

The key words “schizophrenia,” “antipsychotic,” and “neuroleptic” and the drug names “chlorpromazine” and “haloperidol” (typical antipsychotics) and “risperidone” and “olanzapine” (atypical antipsychotics) were used. All phrases related to these keywords were requested using the “explode” command. The bibliographic sections of articles collected during the search were used to direct further inquiries. Cross-referencing of earlier reviews and original studies identified further information.

Studies were included in this meta-analysis if they (1) reported 2 or more assessments of effectiveness, taken at least 7 days apart, in the first 4 weeks of treatment and (2) assessed effectiveness using either the Brief Psychiatric Rating Scale (BPRS)²⁹ or its thought subcomponent (scale rating of item numbers 4 [conceptual disorganization], 12 [hallucinatory behavior], 15 [unusual thought], and 11 [suspiciousness]) or the Posi-

tive and Negative Syndrome Scale (PANSS)³⁰ or its positive subscale (scale rating of item numbers P1-P7). In studies that reported the results graphically only, data were obtained directly from the published graphs.

Studies were excluded from this analysis if they (1) included patients younger than 16 years, (2) were specifically targeted at treatment nonresponders or patients with treatment-resistant schizophrenia, (3) used antipsychotic medications for indications other than psychosis (eg, depressive or anxiety symptoms in a patient with schizophrenia), (4) included simultaneous adjuvant drug therapy (eg, glycine for augmentation of an antipsychotic drug), (5) used sham doses of antipsychotic agents, or (6) included long-acting antipsychotic medications.

DATA EXTRACTION AND STANDARDIZATION

To permit standardized comparisons, knowing that studies use different psychometric scales for rating symptomatic improvement and outcome, we converted measures of response to percentage reduction in symptom severity from baseline. The raw scores were standardized and then were converted to percentages of the baseline scores. This eliminated any difficulties in comparing BPRS and PANSS (and their relevant subcomponent) scores, as well as those arising from the different BPRS scoring conventions across studies. Some studies used a scale from 1 to 7 per question, whereas others used a scale from 0 to 6. These scaling issues were resolved by converting raw scores to standardized scores. Each study created 1 or more symptom response vs time curves, according to the number and different doses of drugs tested. A unit of data in this meta-analysis was a response-time curve for a drug at a given dose. For each measurement, the incremental weekly percentage change in standardized baseline score was calculated.

Owing to the variability in the size of the studies used in this analysis, it was decided to weight each study in the analysis according to the number of patients associated with each measurement. Smaller studies, with results based on fewer patients, were given proportionally less weight than larger studies.

The patient dropout rates for the studies were investigated. Most studies report response on an "as observed basis," but some use a last observation carried forward approach. First, we analyzed these 2 kinds of studies separately. The rate of change in scores over time was not found to be significantly different in the as observed vs the last observation carried forward studies. As a result, we subsequently analyzed the 2 kinds of studies together.

Some studies did not provide sample size information corresponding with each reported time measurement in the study. For these studies, the sample sizes were estimated through a linear regression based on the dropout rates of those studies for which complete information was available. These estimated within-study sample sizes were used in all subsequent analyses wherever true sample sizes were not available.

DATA ANALYSIS

The data were approached with 3 types of analyses. The first analysis included all the studies and examined the effect of antipsychotic drug treatment and placebo treatment on standardized total BPRS or PANSS scores over time. The overall BPRS and PANSS scores contain some items beyond those related specifically to psychotic symptoms. Therefore, to examine the time course of the antipsychotic agents on core psychotic symptoms, a second analysis was carried out using only studies that separately reported data on the BPRS thought subscale and the PANSS positive subscale. Because improvement early in treatment may just reflect nonspecific effects of medications or milieu, this was controlled for by accounting for the degree of im-

provement observed in patients assigned to treatment with placebo. The third analysis examined the data after subtracting the improvement observed with placebo treatment from the total and psychotic subscale scores.

To test whether our findings reveal any evidence of an immediate onset of antipsychotic medication effects, a repeated-measures analysis of covariance was performed on each group of results. The method used for each analysis was identical. Incremental change per week was used as the dependent variable, and time, drug (chlorpromazine, haloperidol, risperidone, or olanzapine), and rating scale (BPRS or PANSS) were included in the model as fixed factors. On completion of the tests, additional contrasts were performed to assess whether the average magnitude of effect within the first 2 weeks after initial treatment was significantly different than the magnitude of the average effect size in weeks 3 and 4. A second series of tests used a repeated-measures analysis of covariance and examined the effect of treatment on total and subscale scores after subtracting the mean placebo effect at each time.

Equations used for (1) calculating standardized scores, (2) estimating attrition of patients from start to end point, and (3) calculating weekly incremental change per week were as follows:

$$(1) \quad \frac{(Y_0 - Y_{\min})}{(Y_{\max} - Y_{\min})} \times 100\%,$$

where Y_0 indicates raw (untransformed) score; Y_{\min} , lower limit of corresponding measurement scale; and Y_{\max} , upper limit of corresponding measurement scale.

$$(2) \quad N_t = N_0 \times (\hat{\beta}_0 + \hat{\beta}_1 \times t),$$

where N_t indicates sample size at time t ; t , time (in days); and $\hat{\beta}_0$, $\hat{\beta}_1$, constants, estimated through weighted least squares regression as

$$\hat{\beta}_1 = \frac{\sum_{i=1}^n w_i X_i Y_i - \frac{\sum_{i=1}^n w_i X_i \sum_{i=1}^n w_i Y_i}{\sum_{i=1}^n w_i}}{\sum_{i=1}^n w_i X_i^2 - \frac{\left(\sum_{i=1}^n w_i X_i\right)^2}{\sum_{i=1}^n w_i}}$$

and

$$\hat{\beta}_0 = \frac{\sum_{i=1}^n w_i Y_i - \hat{\beta}_1 \sum_{i=1}^n w_i X_i}{\sum_{i=1}^n w_i},$$

where Y_i indicates percentage of initial sample remaining on final day of study i ; i , 1- n ; X_i , completion time of study i (in days); and w_i , initial number of patients in study i .

$$(3) \quad Y_w = \frac{X_w - X_{w-1}}{X_0} \times 100\%,$$

where Y_w indicates incremental percentage change in baseline score at week w ; w , 1-4; X_w , standardized score at week w ; and X_0 , standardized baseline score.

SAMPLE CHARACTERISTICS

Forty-two double-masked controlled studies³¹⁻⁷² including 7450 patients were identified. The studies were published between 1976 and 2001, and their duration ranged from 28 to 196 days. Almost 42% of the sample originated from the United States, 19.1% from European countries, and the remainder from non-European and non-North American countries. There were some variations in diagnostic criteria over time: whereas the earlier studies usually used the *International Classification of Diseases* and *Research Diagnostic Criteria for a Selected Group of Functional Disorders* (6.9% of all studies), the newer studies used the *DSM-III-R* and the *DSM-IV* (93.1% of all studies). Nearly 77% of the included studies had washout periods, accounting for 62.8% of the patients included in our meta-analysis. The length of the washout period varied between 1 day (in more recent studies) and 33 days (in earlier studies). Almost half of the studies (47.4%) included only patients with schizophrenia, and the remainder included patients with schizophrenia, schizoaffective disorder, and schizophreniform disorder. The patients were typically in their mid-30s, with an age range of 16 to 72 years (mean, 37.6 years), and 63.8% were male. The average percentage of completers of the studies was 59.5% (at the end point of the study rather than after 4 weeks). Mean age at onset of illness was 25.4 years (range, 9.9-48.8 years), and mean duration of illness was 15.5 years (range, 1-38 years). Mean \pm SD number of previous hospitalizations was 7.1 ± 3.7 . More than half of the studies (52.4%) involved inpatients only, and the remainder included a mixture of inpatients and outpatients. The studies included patients treated with olanzapine (n=3750), haloperidol (n=2447), risperidone (n=896), chlorpromazine (n=95), and placebo (n=262).

TOTAL BPRS AND PANSS SCORES

Figure 2 shows the average trajectory of BPRS and PANSS improvement with the use of antipsychotic drugs vs placebo over time. No significant change in scores over time was observed in the placebo group ($F_{3,13}=1.72$; $P=.22$, representing the main effect of time in the placebo group) in contrast to change in mean total scores in the treatment group ($F_{3,147}=28.94$; $P<.001$, representing the main effect of time in total score test). Post hoc t tests examining differences between the percentage reduction in total scores at weeks 1 to 4 between the treatment and placebo groups revealed that the mean weekly scores for medication differed significantly from those for placebo from the very first week ($P<.05$ after Bonferroni adjustment).

Overall clinical improvement during the first week of antipsychotic drug treatment was significantly greater than that observed in later weeks. The decrease in scores during the first week was almost 3 times as great as the observed effect in weeks 3 and 4 (**Figure 3A**). Bonferroni-adjusted pairwise comparisons revealed that the incremental improvement was significantly greater in the first week than in the second week ($t_{147}=3.80$; $SE=0.69$; $P=.001$), which in turn was greater than in week 3

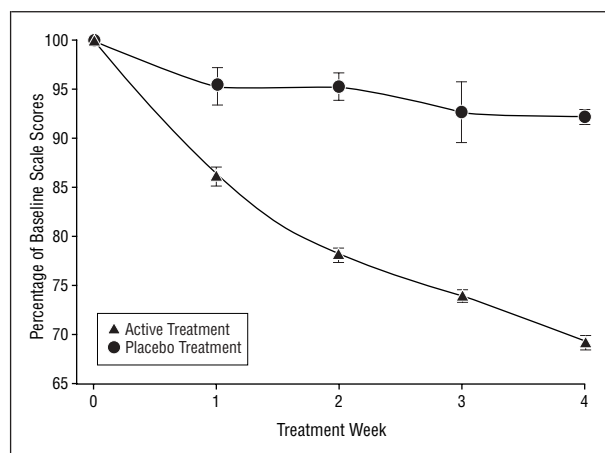


Figure 2. Mean improvement in standardized baseline scores in patients taking antipsychotic drugs vs placebo over time. Error bars represent SE.

($t_{147}=7.22$; $SE=0.73$; $P<.001$) and week 4 ($t_{147}=8.35$; $SE=0.75$; $P<.001$).

To test whether the onset of action of the antipsychotic agents was early vs delayed, tests were undertaken to determine whether greater improvement is seen in the first 2 weeks (per the early-onset hypothesis) or in the next 2 weeks (per the delayed-onset hypothesis). These tests found that the decline in scores within the first 2 weeks of treatment (21.9%) was significantly greater than that observed in the third and fourth weeks (9.8%) ($F_{1,147}=70.51$; $P<.001$).

CORE PSYCHOTIC SYMPTOM SCORES

Change in core psychotic symptoms over time was measured by the change in BPRS thought subscale and PANSS positive subscale scores. Figure 3B shows that the decline in these scores is considerably greater during the first week than in later weeks ($F_{3,30}=5.80$; $P<.01$). As predicted by the early-onset hypothesis, the decline in scores in the first 2 weeks of initial treatment (24.4%) was almost 3 times as much as that observed in the third and fourth weeks (7.7%) ($F_{1,30}=10.58$; $P<.01$).

ACCOUNTING FOR THE PLACEBO EFFECT

To account for the placebo effect, we removed the mean weekly improvement obtained in the placebo-treated group from that in the drug-treated group (**Figure 4A**). After subtracting the placebo group response, the improvement in scores for antipsychotic drugs remained significantly greater in the first week than in the third week ($t_{147}=5.81$; $SE=0.73$; $P<.001$). The improvement in the second week was significantly larger than that in the third week ($t_{147}=7.87$; $SE=0.74$; $P<.001$) and the fourth week ($t_{147}=3.66$; $SE=0.76$; $P<.01$). Improvement in the first 2 weeks (17.2% after subtracting the placebo effect) was significantly higher than that in the subsequent 2 weeks (6.7%; difference: $F_{1,147}=43.74$; $P<.001$). The rate of decline in the core psychotic symptoms after removal of the placebo effect was also greater in the first 2 weeks of treatment (Figure 4B). A contrast of the average effect observed during the first 2 weeks of treatment vs the following

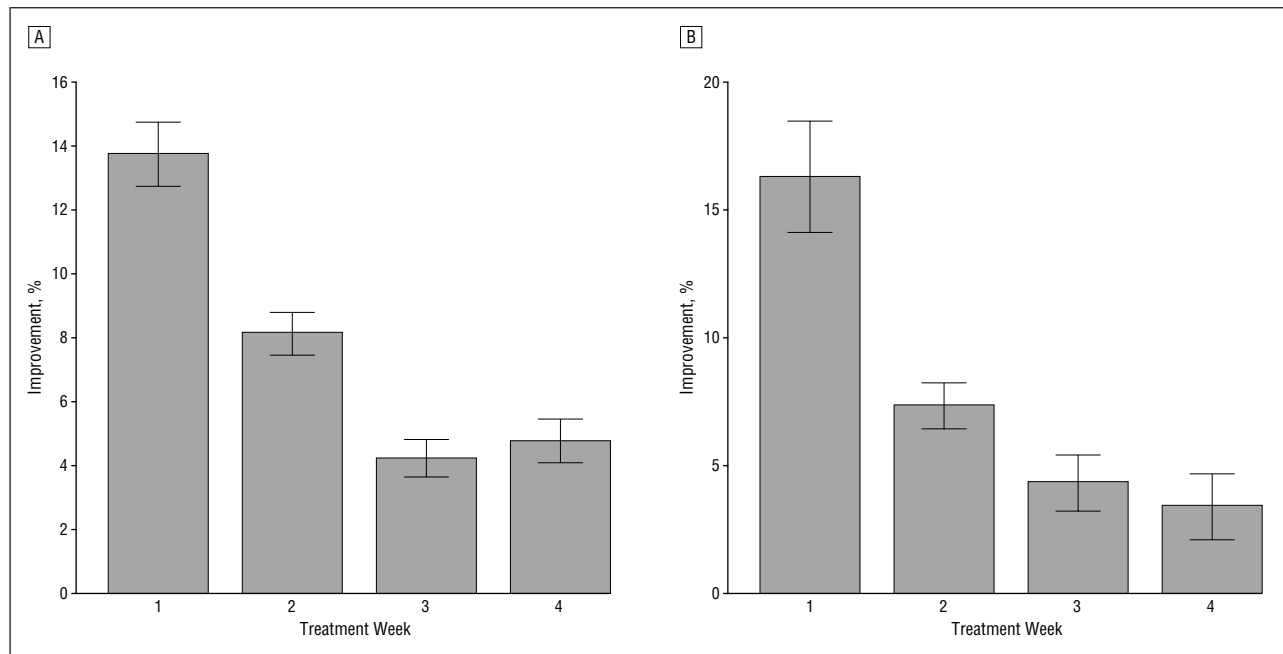


Figure 3. Response to antipsychotic treatment over time. A, Mean overall clinical improvement (total score) ($P < .001$). B, Mean change in core psychotic symptoms ($P < .01$). P values represent the main effect of time. Error bars represent SE.

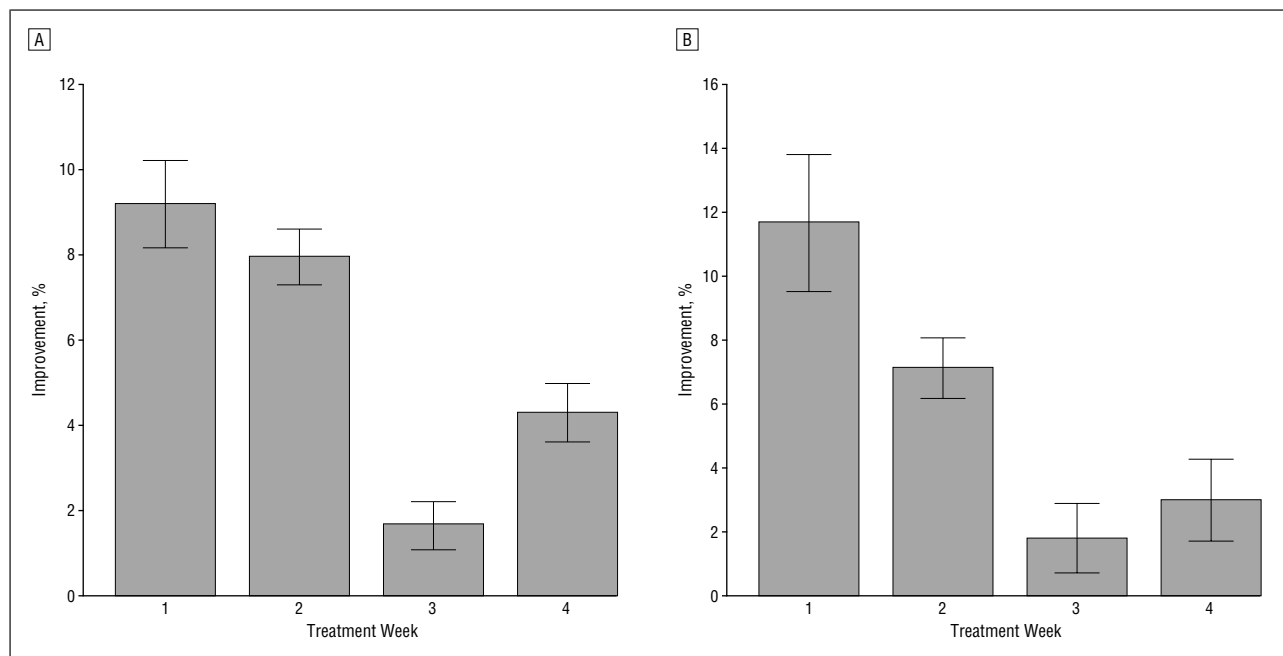


Figure 4. Response to antipsychotic treatment over time after removal of the placebo effect. A, Mean overall clinical improvement ($P < .001$). B, Mean change in core psychotic symptoms ($P = .08$). P values represent the main effect of time. Error bars represent SE.

2 weeks confirms that the psychotic items also show a decidedly early onset of improvement ($F_{1,30} = 6.17$; $P = .02$).

No significant difference among the 4 drugs was found in their impact on subscale scores ($F_{2,7} = 0.31$; $P = .74$) or total scores ($F_{3,54} = 1.49$; $P = .23$).

COMMENT

In this meta-analysis of more than 7400 patients, we found that antipsychotic action starts early after drug adminis-

tration and is cumulative during the ensuing weeks. The empirical data are not consistent with the widely cited delayed-onset hypothesis. Clinical improvement in the first weeks of treatment is often attributed to improvement in nonspecific symptoms such as anxiety and agitation rather than to a change in the core psychotic symptoms. However, even when we restricted the analysis to the BPRS thought and PANSS positive subscales, we observed more improvement in the first 2 weeks than in the next 2 weeks. It is often suggested that improvement in patients with psy-

chosis in the early weeks of treatment results from the inpatient milieu, the effect of adjunctive sedatives, and other nonspecific treatment effects. However, our findings of early onset of action persisted even after we controlled for the degree of change observed in the placebo-treated patients in the same studies. Our findings, which reflect the findings of available double-masked, randomized controlled studies of oral medications, are also consistent with many articles^{28,72-76} in the literature describing improvement in the days immediately after intramuscular antipsychotic drug administration for the acute management of patients with psychosis.

Given this evidence for improvement in psychotic symptoms in the first couple of weeks of treatment, why has the concept of delayed onset been so widely accepted? We think that this may have resulted from confusion between the concept of onset of action vs the time required to achieve a given level of improvement or statistical significance. In almost all of the studies for which we reviewed the curves of antipsychotic response, the antipsychotic group numerically separates from the placebo group in the first measure (usually in the first week). The degree of improvement in the first week (13.8% on average) is smaller than the total cumulative improvement at the end of the third or fourth week (26.1% or 30.8%, respectively). Because most studies are powered to detect a statistically significant effect, they may lack adequate power to declare the early change as significant.

Several limitations of the meta-analytic approach, particularly as we applied it in this study, need to be pointed out. First, we restricted this study to 4 antipsychotic agents (chlorpromazine, haloperidol, risperidone, and olanzapine). We chose these drugs because they represent the most widely used typical antipsychotic agents (haloperidol and chlorpromazine) and the most widely used atypical antipsychotic agents (risperidone and olanzapine).⁷⁷⁻⁷⁹ We choose chlorpromazine to represent the sedating low-potency typical antipsychotic drugs and haloperidol to represent the nonsedating high-potency typical antipsychotic drugs. We found no significant differences in time course among any of these drugs. Thus, we believe that the conclusions we draw about early onset are probably relevant to all antipsychotic drugs.

We analyzed only studies that included more than 1 rating in the first 4 weeks of treatment. In the published literature, some studies do not report data at these early times but only later, such as at 5 or 6 weeks. In the case of chlorpromazine, risperidone, and olanzapine, most studies provided data during the first 4 weeks, so this was not a concern (only 1 study for each drug was excluded). However, in the case of haloperidol, 3 studies were excluded. Comparing the included haloperidol studies (1394 patients) with the excluded haloperidol studies (169 patients) revealed no difference between the 2 sets of studies in terms of degree of response ($t_{16} = -0.36$; $P = .73$). Thus, the exclusion of a few studies is unlikely to have biased the inferences drawn from this meta-analysis.

Although the results of this meta-analysis suggest that patients with schizophrenia in general begin to respond quickly to antipsychotic medication therapy, it is conceivable that the time course for response might vary with such factors as duration of illness, presence or length

of a washout period, and medication dose. Our ability to address these questions was limited by the data available for analysis in these published studies. With the limited data available, we did not find any of these factors to have a significant effect on response trajectory.

While acknowledging these limitations, our findings seem robust and lead us to propose an early-onset hypothesis of antipsychotic action. We propose that there is no notable delay in the onset of antipsychotic action. As threshold concentrations of drug accumulate in the brain during the first few days, the antipsychotic effect begins. The effect does not reach maximal response immediately but accumulates over time, with improvement occurring most rapidly in the first 2 weeks and then slowly reaching a plateau.

The early-onset hypothesis of antipsychotic action has important implications for understanding the process of antipsychotic response and the mechanism of action of antipsychotic drugs. Because it has been assumed that onset is delayed, a search has been ongoing for biological events that are absent in the first few weeks but which appear later. It has been proposed that the depolarization block of dopamine neurons may take place over a period that parallels the delay in onset of clinical improvement that has been assumed to be required.^{12,13,15,17} It has been reported that administration of haloperidol to rats results in a short-term increase in the firing of midbrain dopamine neurons, followed by a decrease in firing—referred to as depolarization block—which takes place after 3 weeks.¹² It has been proposed that the onset of action of antipsychotic agents is related to this decreased firing of the dopamine neurons.^{11,12,14-16} However, this explanation needs to be reconsidered given our finding that the onset of antipsychotic action does not seem to be delayed. There are also other lines of evidence that call into question the clinical relevance of the depolarization block hypothesis. Several studies^{80,81} report failure of haloperidol administration to induce depolarization block of dopamine neurons in unanesthetized rats, raising the possibility that the changes observed in dopamine neuron firing might be an artifact related to general anesthesia.⁸² It is also possible that the depolarization block mechanism underlies antipsychotic response but that it takes place earlier after antipsychotic drug administration than was originally described. White and Wang⁸³ reported a significant decrease in active dopamine cells after 1 week of haloperidol treatment in rats. Further studies are necessary to determine the relationship of dopamine receptor blockade to depolarization block and to establish the time frame over which this phenomenon actually takes place.

The early-onset hypothesis predicts that the mechanism underlying antipsychotic response will involve processes that are relatively early in onset and cumulative over time, paralleling the trajectory of clinical response. In this regard, some interesting new suggestions have been forthcoming. Kuhar and Joyce⁸⁴ recently presented a theoretical model, based on immediate onset and gradual accumulation of protein intermediaries, which may provide a more viable biological underpinning for the nature of antipsychotic response. At a different level of analysis, Miller⁸⁵ and Kapur⁸⁶ suggested that antipsychotic response is akin to psychological extinction or unlearn-

ing, a process that starts immediately and accumulates over time, thus explaining the early onset as well as the delay in maximal effect. It is too early to conclude which of these explanations is most relevant; however, our reconceptualization of the onset of antipsychotic action may point to different underlying mechanisms.

Not only does the early-onset hypothesis affect our models of antipsychotic action, it may also have implications for clinical practice. If the greatest rate of improvement is in the first week of treatment, it raises the possibility that early response to treatment may predict the effectiveness of a drug for a given individual. It has been common clinical practice to treat patients for 4 to 6 weeks with a single medication¹⁰ before deciding whether a given antipsychotic drug is going to be effective for that patient. Although it may take 4 to 6 weeks to get a substantial degree of response, it is an open question whether one has to wait that long to predict whether a patient will respond to that drug. In fact, in the context of antidepressant response, it has been shown that response or nonresponse at the 2-week point is a reliable predictor of 8-week outcome.⁸⁷ The early-onset hypothesis suggests that it may also be possible to determine whether an individual is going to respond to a given dose of antipsychotic medication within the first couple of weeks of treatment.

In summary, we did not find evidence for a delayed onset of antipsychotic action. Instead, we found robust evidence to support an early-onset hypothesis; this hypothesis proposes no notable delay in onset, more improvement in the first week, and a gradual accumulation of improvement toward a plateau.

This early-onset hypothesis provides a new opportunity to investigate the mechanism of action of antipsychotic medication and to evaluate the optimal pharmacologic approach to treating patients with schizophrenia. Future research should test the early-onset hypothesis of antipsychotic action and its implications.

Submitted for publication August 23, 2002; final revision received April 24, 2003; accepted April 24, 2003.

This study was supported by a Canada Research Chair in Schizophrenia and Therapeutic Neuroscience (Dr Kapur), the Tapscott Chair in Schizophrenia Studies at the University of Toronto (Dr Zipursky), and the Ian Douglas Bebessee Fellowship at the Centre for Addiction and Mental Health (Dr Agid).

Corresponding author: Robert Zipursky, MD, Schizophrenia Program, Centre for Addiction and Mental Health, 250 College St, Toronto, Ontario, Canada M5T 1R8 (e-mail: robert_zipursky@camh.net).

REFERENCES

- Frankenburg FR. History of the development of antipsychotic medication. *Psychiatr Clin North Am*. 1994;17:531-540.
- Carlsson A, Lindqvist M. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol Toxicol Copenh*. 1963;20:140-144.
- Seeman P, Lee T. Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science*. 1975;188:1217-1219.
- Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature*. 1976;261:717-719.
- Creese I, Burt DR, Snyder SH. Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. *Science*. 1976;192:481-483.
- Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry*. 2001;50:873-883.
- Gelder MG, López-Ibor JJ, Andreasen N. *New Oxford Textbook of Psychiatry*. New York, NY: Oxford University Press; 2000.
- Marder SR, Van-Kammen DP. Dopamine receptor antagonists. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*. Vol 2. 7th ed. Baltimore, Md: Lippincott Williams & Wilkins; 2000:2356-2377.
- Grace AA, Bunney BS. Electrophysiological properties of midbrain dopamine neurons. In: *Psychopharmacology*. 4th ed. New York, NY: Raven Press; 1995:163-177.
- Van-Kammen DP, Marder SR. Serotonin: dopamine antagonists. In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry*. Vol 2. 7th ed. Baltimore, Md: Lippincott Williams & Wilkins; 2000:2455-2473.
- Grace AA. The depolarization block hypothesis of neuroleptic action: implications for the etiology and treatment of schizophrenia. *J Neural Transm Suppl*. 1992;36:91-131.
- Grace AA, Bunney BS. Induction of depolarization block in midbrain dopamine neurons by repeated administration of haloperidol: analysis using in vivo intracellular recording. *J Pharmacol Exp Ther*. 1986;238:1092-1100.
- Grace AA, Bunney BS, Moore H, Todd CL. Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs. *Trends Neurosci*. 1997;20:31-37.
- Bunney BS. Antipsychotic drug effects on the electrical activity of dopaminergic neurons. *Trends Neurosci*. 1984;7:212-215.
- Bunney BS. Effects of acute and chronic neuroleptic treatment on the activity of midbrain dopamine neurons. *Ann N Y Acad Sci*. 1988;537:77-85.
- Bunney BS, Grace AA. Acute and chronic haloperidol treatment: comparison of effects on nigral dopaminergic cell activity. *Life Sci*. 1978;23:1715-1727.
- Chiodo LA, Bunney BS. Typical and atypical neuroleptics: differential effects of chronic administration on the activity of A9 and A10 midbrain dopaminergic neurons. *J Neurosci*. 1983;3:1607-1619.
- Elkes J, Elkes C. Effects of chlorpromazine on the behaviour of chronically overactive psychotic patients. *BMJ*. 1954;2:560-565.
- Winkelman NW. Chlorpromazine in the treatment of neuropsychiatric disorders. *JAMA*. 1954;155:18-21.
- Stern RG, Kahn RS, Davidson M, Nora RM, Davis KL. Early response to clozapine in schizophrenia. *Am J Psychiatry*. 1994;151:1817-1818.
- Stern RG, Kahn RS, Harvey PD, Amin F, Apter SH, Hirschowitz J. Early response to haloperidol treatment in chronic schizophrenia. *Schizophr Res*. 1993;10:165-171.
- McDermott BE, Sautter FJ, Garver DL. Heterogeneity of schizophrenia: relationship to latency of neuroleptic response. *Psychiatry Res*. 1991;37:97-103.
- Garver DL, Kelly K, Fried KA, Magnusson M, Hirschowitz J. Drug response patterns as a basis of nosology for the mood-incongruent psychoses (the schizophrenias). *Psychol Med*. 1988;18:873-885.
- Anderson WH, Kuehne JC, Catanzano DM. Rapid treatment of acute psychosis. *Am J Psychiatry*. 1976;133:1076-1078.
- Donlon PT, Tupin JP. Rapid "digitalization" of decompensated schizophrenic patients with antipsychotic agents. *Am J Psychiatry*. 1974;131:310-312.
- Glovinsky D, Kirch DG, Wyatt RJ. Early antipsychotic response to resumption of neuroleptics in drug-free chronic schizophrenic patients. *Biol Psychiatry*. 1992;31:968-970.
- Lerner Y, Lwow E, Levitin A, Belmaker RH. Acute high-dose parenteral haloperidol treatment of psychosis. *Am J Psychiatry*. 1979;136:1061-1064.
- Neborsky R, Janowsky D, Munson E, Depry D. Rapid treatment of acute psychotic symptoms with high- and low-dose haloperidol: behavioral considerations. *Arch Gen Psychiatry*. 1981;38:195-199.
- Overall JEG. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10:799-812.
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261-276.
- Ahlfors UG, Rimon R, Appelberg B, Hagert U, Harma P, Katila H, Mahlanen A, Mehtonen OP, Naukkarinen H, Outakoski J, et al. Remoxipride and haloperidol in schizophrenia: a double-blind multicentre study. *Acta Psychiatr Scand Suppl*. 1990;358:99-103.
- Andersen J, Korner A, Ostergaard P, Fensbo C, Birket-Smith M, Thiesen S, Hansen NR, Fogh M, Kristensen M, Moller-Nielsen EM, et al. A double blind comparative multicentre study of remoxipride and haloperidol in schizophrenia. *Acta Psychiatr Scand Suppl*. 1990;358:104-107.
- Beasley CM Jr, Hamilton SH, Crawford AM, Dellva MA, Tollefson GD, Tran PV, Blin O, Beuzen JN. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol*. 1997;7:125-137.
- Beasley CM Jr, Sanger T, Satterlee W, Tollefson G, Tran P, Hamilton S. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. *Psychopharmacology (Berl)*. 1996;124:159-167.
- Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology*. 1996;14:111-123.
- Blin O, Azorin JM, Bouhours P. Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. *J Clin Psychopharmacol*. 1996;16:38-44.
- Borison RL, Pathiraja AP, Diamond BI, Meibach RC. Risperidone: clinical safety and efficacy in schizophrenia. *Psychopharmacol Bull*. 1992;28:213-218.

38. Borison RL, Sinha D, Haverstock S, McLarnon MC, Diamond BI. Efficacy and safety of tiospirone vs haloperidol and thioridazine in a double-blind, placebo-controlled trial. *Psychopharmacol Bull.* 1989;25:190-193.
39. Brannen JO, McEvoy JP, Wilson WH, Petrie WM, Ban TA, Berney SA, Schaffer JD. A double-blind comparison of bromperidol and haloperidol in newly admitted schizophrenic patients. *Pharmacopsychiatry.* 1981;14:139-140.
40. Carriere P, Bonhomme D, Lemperiere T. Amisulpride has a superior benefit/risk profile to haloperidol in schizophrenia: results of a multicentre, double-blind study (the Amisulpride Study Group). *Eur Psychiatry.* 2000;15:321-329.
41. Ceskova E, Svestka J. Double-blind comparison of risperidone and haloperidol in schizophrenic and schizoaffective psychoses. *Pharmacopsychiatry.* 1993;26:121-124.
42. Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, Labelle A, Beaulclair L, Arnott W. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol.* 1993;13:25-40.
43. Claus A, Bollen J, De Cuyper H, Eneman M, Malfroid M, Peuskens J, Heylens S. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. *Acta Psychiatr Scand.* 1992;85:295-305.
44. Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Am J Psychiatry.* 2001;158:765-774.
45. Cooper SJ, Tweed J, Raniwalla J, Butler A, Welch C. A placebo-controlled comparison of zotepine versus chlorpromazine in patients with acute exacerbation of schizophrenia. *Acta Psychiatr Scand.* 2000;101:218-225.
46. Copolov DL, Link CG, Kowalcyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, "Seroquel") and haloperidol in schizophrenia. *Psychol Med.* 2000;30:95-105.
47. Delcker A, Schoon ML, Oczkowski B, Gaertner HJ. Amisulpride versus haloperidol in treatment of schizophrenic patients: results of a double-blind study. *Pharmacopsychiatry.* 1990;23:125-130.
48. Den Boer JA, Ravelli DP, Huisman J, Ohrvik J, Verhoeven WM, Westenberg HG. Double blind comparative study of remoxipride and haloperidol in acute schizophrenic patients. *Psychopharmacology.* 1990;102:76-84.
49. Deo R, Soni S, Rastogi SC, Levine S, Plant I, Edwards JG, Mitchell M, Chanas A. Remoxipride and haloperidol in the acute phase of schizophrenia: a double-blind comparison. *Acta Psychiatr Scand Suppl.* 1990;358:120-124.
50. Ericksen SE, Hurt SW, Chang S. Haloperidol dose, plasma levels, and clinical response: a double-blind study [proceedings]. *Psychopharmacol Bull.* 1978;14:15-16.
51. Fleischhacker WW, Barnas C, Stuppach CH, Unterweger B, Miller C, Hinterhuber H. Zotepine vs haloperidol in paranoid schizophrenia: a double-blind trial. *Psychopharmacol Bull.* 1989;25:97-100.
52. Gelenberg AJ, Doller JC. Clozapine versus chlorpromazine for the treatment of schizophrenia: preliminary results from a double-blind study. *J Clin Psychiatry.* 1979;40:238-240.
53. Gerlach J, Behnke K, Heltberg J, Munk-Anderson E, Nielsen H. Sulpiride and haloperidol in schizophrenia: a double-blind cross-over study of therapeutic effect, side effects and plasma concentrations. *Br J Psychiatry.* 1985;147:283-288.
54. Haas S, Beckmann H. Pimozide versus haloperidol in acute schizophrenia: a double blind controlled study. *Pharmacopsychiatry.* 1982;15:70-74.
55. Hebenstreit GF, Laux G, Schubert H, Beckmann H, Amman J, Bunse J, Eikmeier G, Geretsegger C, Kanitz RD, Kanzow WT, et al. A double-blind comparative multicentre study of controlled-release remoxipride, immediate-release remoxipride and haloperidol in schizophrenia. *Pharmacopsychiatry.* 1991;24:153-158.
56. Hoyberg OJ, Fensbo C, Remvig J, Lingjaerde O, Sloth-Nielsen M, Salvesen I. Risperidone versus perphenazine in the treatment of chronic schizophrenic patients with acute exacerbations. *Acta Psychiatr Scand.* 1993;88:395-402.
57. Ishigooka J, Inada T, Miura S. Olanzapine versus haloperidol in the treatment of patients with chronic schizophrenia: results of the Japan multicenter, double-blind olanzapine trial. *Psychiatry Clin Neurosci.* 2001;55:403-414.
58. Itoh H. A comparison of the clinical effects of bromperidol, a new butyrophenone derivative, and haloperidol on schizophrenia using a double-blind technique. *Psychopharmacol Bull.* 1985;21:120-122.
59. Klieser E, Strauss WH, Lemmer W. The tolerability and efficacy of the atypical neuroleptic remoxipride compared with clozapine and haloperidol in acute schizophrenia. *Acta Psychiatr Scand Suppl.* 1994;380:68-73.
60. Lapiere YD, Nair NP, Chouinard G, Awad AG, Saxena B, Jones B, McClure DJ, Bakish D, Max P, Manchanda R, et al. A controlled dose-ranging study of remoxipride and haloperidol in schizophrenia: a Canadian multicentre trial. *Acta Psychiatr Scand Suppl.* 1990;358:72-77.
61. Laux G, Klieser E, Schroder HG, Dittman V, Unterweger B, Schubert H, Konig P, Schony HW, Bunse J, Beckmann H. A double-blind multicentre study comparing remoxipride, two and three times daily, with haloperidol in schizophrenia. *Acta Psychiatr Scand Suppl.* 1990;358:125-129.
62. Lindstrom LH, Wieselgren IM, Struwe G, Kristjansson E, Akselson S, Arthur A, Andersen T, Lindgren S, Norman O, Naimell L, et al. A double-blind comparative multicentre study of remoxipride and haloperidol in schizophrenia. *Acta Psychiatr Scand Suppl.* 1990;358:130-135.
63. Mendlewicz J, de Bleeker E, Cosyns P, Deleu G, Lotstra F, Masson A, Mertens C, Parent M, Peuskens J, Suy E, et al. A double-blind comparative study of remoxipride and haloperidol in schizophrenic and schizophreniform disorders. *Acta Psychiatr Scand Suppl.* 1990;358:138-141.
64. Moller HJ, Boyer P, Fleurot O, Rein W. Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison with haloperidol: PROD-ASLP Study Group. *Psychopharmacology (Berl).* 1997;132:396-401.
65. Patris M, Agussol P, Alby JM, Brion S, Burnat G, Castelnaud D, Deluermoz S, Dufour H, Ferreri M, Goudemand M, et al. A double-blind multicentre comparison of remoxipride, at two dose levels, and haloperidol. *Acta Psychiatr Scand Suppl.* 1990;358:78-82.
66. Peuskens J, Bech P, Moller HJ, Bale R, Fleurot O, Rein W. Amisulpride vs risperidone in the treatment of acute exacerbations of schizophrenia: Amisulpride Study Group. *Psychiatry Res.* 1999;88:107-117.
67. Pflug B, Bartels M, Bauer H, Bunse J, Gallhofer B, Haas S, Kanzow WT, Klieser E, Kufferle B, Stein D, et al. A double-blind multicentre study comparing remoxipride, controlled release formulation, with haloperidol in schizophrenia. *Acta Psychiatr Scand Suppl.* 1990;358:142-146.
68. Selman FB, McClure RF, Helwig H. Loxapine succinate: a double-blind comparison with haloperidol and placebo in acute schizophrenics. *Curr Ther Res Clin Exp.* 1976;19:645-652.
69. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, Graffeo KA, Thieme ME. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry.* 1997;154:457-465.
70. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C Jr, Tollefson GD. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol.* 1997;17:407-418.
71. Tuason VB, Escobar JI, Garvey M, Schiele B. Loxapine versus chlorpromazine in paranoid schizophrenia: a double-blind study. *J Clin Psychiatry.* 1984;45:158-163.
72. Wright P, Birkett M, David SR, Meehan K, Ferchland I, Alaka KJ, Saunders JC, Krueger J, Bradley P, San L, Bernardo M, Reinstein M, Braier A. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatry.* 2001;158:1149-1151.
73. Bechelli LP, Navas-Filho F. Short-term double-blind trial of pipothiazine palmitate and haloperidol in the acute phase of schizophrenia. *Encephale.* 1986;12:121-125.
74. Fruensgaard K, Korsgaard S, Jorgensen H, Jensen K. Loxapine versus haloperidol parenterally in acute psychosis with agitation: a double-blind study. *Acta Psychiatr Scand.* 1977;56:256-264.
75. Tuason VB. A comparison of parenteral loxapine and haloperidol in hostile and aggressive acutely schizophrenic patients. *J Clin Psychiatry.* 1986;47:126-129.
76. Paprocki J, Versiani M. A double-blind comparison between loxapine and haloperidol by parenteral route in acute schizophrenia. *Curr Ther Res Clin Exp.* 1977;21:80-100.
77. IMS Health. *Pharmaceutical Information 2001.* IMS Health Web site, 2001. Available at: www.imshealth.com. Accessed July 28, 2003.
78. Wysowski DK, Baum C. Antipsychotic drug use in the United States, 1976-1985. *Arch Gen Psychiatry.* 1989;46:929-932.
79. Hermann RC, Yang D, Ettner SL, Marcus SC, Yoon C, Abraham M. Prescription of antipsychotic drugs by office-based physicians in the United States, 1989-1997. *Psychiatr Serv.* 2002;53:425-430.
80. Mereu G, Lilliu V, Vargiu P, Muntoni AL, Diana M, Gessa GL. Failure of chronic haloperidol to induce depolarization inactivation of dopamine neurons in unanesthetized rats. *Eur J Pharmacol.* 1994;264:449-453.
81. Melis M, Mereu G, Lilliu V, Quartu M, Diana M, Gessa GL. Haloperidol does not produce dopamine cell depolarization-block in paralyzed, unanesthetized rats. *Brain Res.* 1998;783:127-132.
82. Mereu G, Lilliu V, Vargiu P, Muntoni AL, Diana M, Gessa GL. Depolarization inactivation of dopamine neurons: an artifact? *J Neurosci.* 1995;15:1144-1149.
83. White FJ, Wang RY. Comparison of the effects of chronic haloperidol treatment on A9 and A10 dopamine neurons in the rat. *Life Sci.* 1983;32:983-993.
84. Kuhar MJ, Joyce AR. Slow onset of CNS drugs: can changes in protein concentration account for the delay? *Trends Pharmacol Sci.* 2001;22:450-456.
85. Miller R. The time course of neuroleptic therapy for psychosis: role of learning processes and implications for concepts of psychotic illness. *Psychopharmacology.* 1987;92:405-415.
86. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology and pharmacology in schizophrenia. *Am J Psychiatry.* 2002;160:13-23.
87. Nierenberg AA, McLean NE, Alpert JE, Worthington JJ, Rosenbaum JF, Fava M. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. *Am J Psychiatry.* 1995;152:1500-1503.