

Antipsychotic Maintenance Treatment for Patients With Schizophrenia: The Need for Placebo-Controlled Trials and The Risk of Paradigm Shifts

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Background and Hypothesis: There is limited evidence guiding clinicians and patients on how long to continue antipsychotic medication beyond the first 1–2 years of treatment. Data from long-term (beyond 2 years) placebo-controlled trials would be informative but would be resource-intensive and technically difficult to obtain. Philosophy and history offer perspective on whether schizophrenia researchers should invest in such trials. **Study Design:** Essay. **Results:** In Descartes' model of science, knowledge grows by accumulation and evolves from simpler toward more complex areas. From this perspective, the most important questions are when and how to build this evidence base. In Kuhn's model of science, paradigm shifts can occur that reframe which questions and answers are meaningful. From this perspective, the question of whether to invest in long-term placebo-controlled trials is especially important. An historical review of schizophrenia over the past century indicates that major paradigm shifts have occurred regarding schizophrenia treatments, what counts as evidence, and the definition of schizophrenia. **Conclusions:** While long-term placebo-controlled trials would add value within the current paradigm, if a paradigm shift occurs there is a risk that this value would not be maintained in the new paradigm.

Key words: antipsychotics/maintenance/treatment/patients/schizophrenia/placebo-controlled trials

Introduction

For decades, psychiatry has wrestled with the question of how long persons with schizophrenia should continue antipsychotic medication (D2 receptor antagonists).^{1,2} Treatment guidelines from the World Federation of Societies of Biological Psychiatry,³ the National Institute for Health and Care Excellence,⁴ the Royal Australian

and New Zealand College of Psychiatrists,⁵ and the Canadian Schizophrenia Guidelines⁶ have generally recommended continuous antipsychotic treatment for at least the first 1–2 years after a psychotic episode or exacerbation, sometimes extending this to 5 years or longer in specific circumstances. However, authors caution that “Recommendations for treatment durations in schizophrenia do not have a strong empirical basis and further studies are needed to provide better evidence-based recommendations” (p. 13).³ also⁷ Notably, the most recent guidelines from the American Psychiatric Association⁸ recommend maintenance medication without recommending specific time intervals, instead emphasizing frequent review of the pros and cons in the context of shared decision-making.

The decision of whether to continue antipsychotic medication after a period of stability has significant implications. Continuing antipsychotic medication long-term can involve numerous adverse effects (eg, tardive dyskinesia, Parkinsonism, sedation, weight gain, diabetes), financial burden, inconvenience, and stigma, without necessarily preventing relapse or halting disease progression.^{9–12} Alternatively, stopping antipsychotic medication can increase the risk of relapse, which may result in hospitalization, unsafe behaviors, personal distress, social/interpersonal disruption, and by some accounts an increased risk of refractory symptoms.^{13,14} Complicating this decision is an awareness that while antipsychotic medication helps many patients achieve remission or maintain symptom stability (at least with respect to some symptom domains, eg, positive symptoms, disorganization, affective symptoms),¹⁵ some patients do well (or as well) without continuous medication,^{16,17} some remain symptomatic despite continuous medication,¹⁸ and there is currently no evidence-based way to predict reliably and

specifically whether a patient belongs to 1 category or another.⁷

The existing literature is conspicuously lacking double-blind, randomized, placebo-controlled trials to guide treatment decisions beyond the first 2 years.⁷ Building such an evidence base could have enormous benefit, potentially affecting every patient with schizophrenia at 1 point or another. However, there are important reasons why these studies have not been conducted. The pragmatic challenges are formidable, especially: generating consensus on outcome measures, defining and recruiting a sufficiently homogenous population, establishing and maintaining adherence to a protocol, retaining enough subjects to generate meaningful results, and replicating core findings. Nevertheless, these challenges might be surmountable with sufficient resources and sufficient time.

This essay will focus less on the technical questions surrounding whether psychiatry *could* meaningfully study antipsychotic maintenance treatment via long-term, double-blind, randomized, placebo-controlled trials. Rather, it will consider the ethical question of whether psychiatry *should*. To be ethical (and feasible) the benefits must compare favorably against risks and costs. How long the potential benefits will last is an important consideration that has received little attention to date. Will benefits endure, or will schizophrenia research change in ways that render the findings less relevant, harder to apply, or otherwise less beneficial than originally hoped? To develop this question, this essay will look to two contrasting perspectives on science, one proposed by René Descartes and the other by Thomas Kuhn, while looking also to the history of medicine and the history of schizophrenia in particular.

Descartes—Discourse on Method

René Descartes (1596–1650), in his *Discourse on the Method of Rightly Conducting the Reason and Seeking for Truth in the Sciences*,¹⁹ articulated a method that enormously influenced the sciences during subsequent centuries, and which contemporary scientists will recognize as central to the scientific method. In Part II Descartes recommended 4 precepts:

The first of these was to accept nothing as true which I did not clearly recognize to be so... The second was to divide up each of the difficulties which I examined into as many parts as possible... The third was to carry on my reflections in due order, commencing with objects that were the most simple and easy to understand, in order to rise little by little, or by degrees, to knowledge of the most complex... The last was in all cases to make enumerations so complete and reviews so general that I should be certain of having omitted nothing. (p. 13)¹⁹

Using this method, Descartes hoped “there can be nothing so remote that we cannot reach to it, nor so recalcitrant that we cannot discover it” (p. 13).¹⁹

Placing the central question (how long to continue antipsychotic medication) within this intellectual tradition gives it a particular framing. The question is readily viewed as a component of the larger moral and scientific question of how best to care for persons with schizophrenia. The question assumes increasing importance as less-complex questions are answered, maybe even taking on an air of inevitability. That the path will be potentially costly and challenging is not necessarily problematic; Descartes’ framework anticipated some steps being more resource intensive than others. Moreover, those who engage in the undertaking, both researchers and subjects, may believe with good reason that their efforts are contributing to an enduring body of knowledge about schizophrenia and its treatment. The central debate, from this perspective, is not whether to invest in this line of research, but how and when.

Kuhn—The Structure of Scientific Revolutions

Thomas Kuhn (1922–1996) proposed a very different view of science, one that challenged the notion that science progresses through the accumulation of facts, theories, and laws. In *The Structure of Scientific Revolutions*,²⁰ he proposed that each age is dominated by a paradigm. This paradigm organizes a scientific field, indicates which questions are meaningful, and restricts what will count as answers. Adherents, accepting the paradigm and working within it, engage in “normal science,” or a series of puzzle-solving endeavors intended to work out the various implications of the paradigm. Importantly, no paradigm is complete, and normal science eventually produces anomalies (observations that cannot be reconciled with the paradigm). When these anomalies can no longer be ignored there is a crisis and a period of “extraordinary science” during which a new paradigm is forged. This new paradigm is gradually accepted, beginning a new cycle.

In Kuhn’s model, both questions and answers are contingent on the paradigm, and when the paradigm changes, so do the questions and answers that people care about. In contrast to Descartes’ optimism that “there can be nothing so remote that we cannot reach to it, nor so recalcitrant that we cannot discover it” (p. 13),¹⁹ Kuhn’s model predicts that many questions will go forever unanswered; either because the answers are unattainable within the current paradigm (anomalies), or because a paradigm shift occurs before specific puzzles have been solved. Moreover, even when questions are answered there is no guarantee that the answers or indeed the questions themselves will be relevant in the new paradigm.

From this perspective, planning and developing new lines of research—especially research involving complex issues such as how long to continue antipsychotic medication—must consider not only pragmatic questions about how and when, but also the overarching question of whether to pursue this line of research. Kuhn’s model

predicts that not all questions have answers, and not all answers endure.

Paradigm Shifts: Examples

The history of schizophrenia in the 20th century has some important examples of paradigm shifts: the introduction of antipsychotic medication, the introduction of randomized controlled trials, and periodic revisions to diagnostic nomenclature. At each transition the questions people asked and the answers they accepted fundamentally changed.

Introduction of Antipsychotic Medication

The discovery of antipsychotic medication brought about a paradigm shift in how psychiatrists thought about schizophrenia treatment. In a superficial sense, it is self-evident that psychiatrists did not ask how long to continue antipsychotic medication before there was antipsychotic medication. More deeply, a review of period textbooks captures a fundamental reconceptualization of schizophrenia and its treatment.

Eugene Bleuler, Textbook of Psychiatry (1924). Decades before the discovery of antipsychotic medications, in his *Textbook of Psychiatry*,²¹ Eugene Bleuler (1857–1939) considered short-term asylum-based treatment to be the core intervention. He believed, “Most schizophrenics are not to be treated at all, or at any rate outside of asylums” (p. 443). Beyond this he claimed, “the supreme remedy ... is training for work under conditions that are as normal as possible” (p. 443), as well as providing practical support for individuals living in the community (p. 445).

Bleuler’s textbook mentions only a few instances where medication might be helpful: bromide for “general nervous excitability” and Hyoscine (scopolamine), morphine, and Somnifen (a barbiturate) for feeding malnourished persons (p. 444).

Wendell Muncie, Psychobiology and Psychiatry: A textbook of Normal and Abnormal Human Behavior, 2nd Edition (1948). Just a few years before the discovery of chlorpromazine, Wendell Muncie (b. 1897) published his textbook.²² Muncie was a psychiatrist affiliated with Johns Hopkins University and his textbook carried an endorsement from Adolph Meyer (1866–1950).

Muncie promoted a psychodynamic view of schizophrenia, describing its symptoms as bizarre reactions to stressful circumstances or psychological conflicts. The disease might be precipitated by conflicts involving sexuality, religion, ethics, philosophy, ambitions, life goals, marital adjustment, and the “competitive situation in the struggle for existence” (p. 397). Acute symptoms could become chronic due to “the increasing weight of the habits formed in the acute phase: emotional habits,

habits of thinking, management of the instinctual urges” (p. 399). He considered psychodynamic psychotherapy to be the foundation of treatment.

Muncie developed a longer list of medications and indications than what Bleuler presented, describing approximately 10 medications including morphine and alcohol (the latter of which he did not recommend). His concept of what psychiatric medication could do was limited to “reducing tension states, motor unrest, mental turmoil, and insomnia” (p. 533), a conceptualization that was reasonable given the available formulary, but that also relegated medication to a minor or peripheral role in schizophrenia treatment.

Jack Ewalt and Dana Farnsworth, Textbook of Psychiatry (1963). In 1963, a decade into the antipsychotic era, Jack Ewalt (1910–1998) and Dana Farnsworth (1905–1986), both Harvard psychiatrists, published a textbook of psychiatry.²³ Their primary orientation was explicitly psychoanalytic, holding that schizophrenia originates from disrupted early relationships, leading the person to respond to later realities with the emotions and thought processes of the infant ego and regression to the state of primary narcissism (p. 213). They framed symptoms of schizophrenia (eg, delusions, hallucinations, disorganization) as expressions of anxiety or aggression, or as defense against emotional connections with others (p. 214–218).

Importantly, they describe medication as having a major role, but they framed this role as subservient to psychodynamic aims.

...the physician needs a well-organized therapeutic plan. An early decision must be made about the depth and intensity of the psychotherapy: will the goal be to uncover the basic conflict material and aid in development of a stronger ego, or will the goal be social manipulation and ego support? ...Ego support and rehabilitation is the basic technique; it should be used with all patients and comes in many forms... The tranquilizing drugs also play a major role in ego support. They seem to be the most effective way of reducing stress so that the patient can cope with his environment without the need to regress into psychotic behavior. Patients who escape from interaction with family, other patients, and personnel through psychotic behavior often respond to ataractic [antipsychotic] drugs by resuming behavior that is reasonably near normal. They can often enter into meaningful therapeutic relationships that are too threatening without the chemical support. (p. 226)

Ewalt and Farnsworth acknowledge debate between psychotherapists and psychopharmacologists about which method yields better outcomes, and attempt to strike a compromise.

There are psychiatrists, and the authors are among them, who believe that intensive, dynamic psychotherapy in conjunction with the ego-supportive methods outlined above

(including drugs) will give a particular patient the best chance for recovery or significant improvement. (p. 227)

Freedman, Kaplan, and Sadock, Modern Synopsis of Comprehensive Textbook of Psychiatry (1972). A decade later Alfred Freedman (1917–2011), Harold Kaplan (1927–1998), and Benjamin Sadock (b. 1933) published an influential textbook that subsequently went through many editions.²⁴ In it they credit antipsychotic medication as the best treatment available for schizophrenia.

Major tranquilizers deserve most credit for the 30 per cent decline in the resident schizophrenic population during the past 15 years. Haloperidol deserves special mention in the treatment of chronic schizophrenic patients. Phenothiazines [sic] today are considered the best treatment available for schizophrenia. (p. 247)

Notably, they seem to arrive at this statement reluctantly. Earlier in their chapter on schizophrenia they write about biological theories of schizophrenia dismissively: “Perhaps the theory most stubbornly clung to states that schizophrenia is an organic disease resulting from a morphological or functional defect in some organ system, perhaps the brain” (p. 227). They devote the bulk of their chapter to psychological theories of schizophrenia (p. 221–225) and psychotherapies (p. 241–246). Organic therapies are discussed briefly at the end (p. 246–247), with the above quotation appearing—somewhat from nowhere—at the very end of the chapter.

As these texts illustrate, the introduction of antipsychotic medication led to a paradigm shift in schizophrenia treatment, during which asylum care and psychodynamic therapies were replaced by antipsychotic medication as the foundation for treatment. Psychiatric hospitals and psychotherapies continued to have important roles, but these roles were dramatically changed from what they had been.

Introduction of Randomized Controlled Clinical Trials

Medicine did not always look to randomized controlled trials for guidance on best practices. Rather, medicine’s gradual embrace of quantification, statistics, and clinical trials in the twentieth century was a paradigm shift. In his book, *Quantification and the Quest for Medical Certainty*, historian J. Rosser Matthews retraces the contentious debates—spanning centuries—over whether medicine was to be an art (emphasizing clinical experience, personal skill and judgment, and the unique attributes of individual patients) or a science (emphasizing empirical measurements, statistical analysis, repeatable results, generalizability, and aggregate assessments).²⁵ Matthews’ narrative culminates with the first randomized controlled trial, published in 1948,²⁶ and concludes with explicit references to Kuhn and paradigm shifts.

Importantly, randomized controlled trials began appearing in the medical literature at nearly the same

time as the first antipsychotic medications. It took time for psychiatry to adapt to both innovations; to embrace them and to develop best practices. In 1975, one of the earliest reviews of antipsychotic maintenance therapy in schizophrenia summarized this recent evolution in methodology.

Initially a host of uncontrolled studies appeared, reporting the finding that maintenance medication decreased the frequency of relapse. Subsequently 24 controlled studies comparing the relapse rates of patients on placebo and maintenance neuroleptics have appeared in the literature. In my judgment the double-blind controlled studies provide the best evidence of efficacy. The earlier studies on maintenance medication were initiated early in the era of phenothiazines, when sophisticated methodology for controlled investigation had not been completely worked out. These studies performed a pioneering function in the development of quantitative, double-blind research designs, but the methodology used was not so refined as it has been in studies carried out more recently, when much more sophisticated techniques were available. (p. 1237)¹

Many researchers who conducted these early trials were explicitly critical of previous research methods and deliberate in forging improved methods. Good et al.²⁷ and Gross²⁸ both conducted their trials because existing evidence was limited to clinical impressions and opinions. Diamond and Marks²⁹ as well as Blackburn and Allen³⁰ conducted their trials in part because of a prior study that had no control group. Caffey et al.³¹ believed earlier studies had misinterpreted key findings and mishandled study dropouts. Leff and Wing³² expressed multiple criticisms of prior studies, including inherent bias in the design and failing to measure treatment adherence. Hogarty et al.³³ and Chouinard et al.³⁴ criticized studies for enrolling diagnostically and prognostically mixed patient groups. Rifkin et al.³⁵ noted that previous studies did not analyze samples with regard to remission status. Andrews et al.³⁶ and Wistedt³⁷ provide long lists of methodological limitations in previous literature and propose to overcome them. While some of this might be self-justification, common in scientific writing, there is little question that trials were becoming more rigorous and sophisticated.

It would be fair to debate whether clinical trials methodology has reached maturity, stabilizing around best practices, versus how much it will continue to evolve. However, the lesson from history is that methods of reasoning—what count as compelling justifications—can change. Evidence and arguments that triumph one day can, at a later date, appear far less compelling.

Revisions of Diagnostic Nomenclature

Periodic changes in psychiatric diagnoses have also functioned at the level of a paradigm shift. Michael First,

a leader in the development of multiple editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) credits the original DSM, published in 1952, with introducing a paradigm shift.³⁸ It standardized a diagnostic vocabulary for a generation of psychiatrists who were less embedded in public mental health hospitals where psychotic illnesses and Kraepelinian models dominated. It also made psychodynamic and psychosocial theories of psychopathology central to diagnosis and treatment.

Decades later the DSM-III, published in 1980, introduced another paradigm shift.³⁸ It was created in response to criticism that psychiatric diagnoses had poor interrater reliability, and in response to psychiatry's need to conduct clinical trials evaluating a growing formulary of psychiatric medications. It introduced a now-familiar symptom-based approach that equated visible and measurable symptoms with the presence of disease. While it remained theory-neutral regarding etiology, there was hope that it would help psychiatric researchers advance toward greater understanding of etiology and pathophysiology.

When preparations for the DSM-5 began in 1999 there was hope that it would initiate another paradigm shift; introducing a diagnostic system based not on descriptions of symptoms but on etiology and pathophysiology.³⁸ Unfortunately, early feedback from workgroups indicated there was insufficient understanding of the etiology and pathophysiology of mental disorders to justify replacing the descriptive approach, and that—while the DSM-5 could be groundbreaking in many respects—this particular paradigm shift would have to wait.

While changes in diagnostic criteria can have good reasons behind them, they can also be disruptive to patients, clinicians, and researchers. Psychiatrists studying maintenance treatment in the 1970s complained about how difficult it was to interpret and compare clinical trials that used different diagnostic criteria.^{32,36,37} Spitzer et al. advised in advance of publication that the DSM-III made several substantive changes to the schizophrenia diagnosis, and that many individuals diagnosed with schizophrenia under DSM-II would receive a different diagnosis in the DSM-III (eg, paranoid disorder, schizoaffective disorder, affective disorder).³⁹

It is hard to predict when the next diagnostic paradigm shift will occur, but easy to forecast that research using a new diagnostic paradigm will be difficult to reconcile with the current evidence base. If schizophrenia is redefined as several different disorders, or if biomarkers reveal different subtypes that respond to different treatments, research based on the former diagnostic criteria will appear outdated and potentially irrelevant.

Discussion

Descartes and Kuhn provide contrasting views of science, which generate very different assessments of

research proposals involving long-term, double-blind, randomized, placebo-controlled trials of antipsychotic medication in schizophrenia. From Descartes' perspective, moving into this line of research—or at least seriously considering it—would be appropriate, desirable, and maybe inevitable. Many less-complicated questions have already been addressed by short-term acute treatment trials⁴⁰ and longer-term relapse prevention trials.^{7,15,41} At some point, conducting even longer clinical trials to inform antipsychotic treatment beyond 2 years would become the next priority (assuming the trials are feasible).

Alternatively, Kuhn's observation that science undergoes paradigm shifts, during which questions and answers both change, suggests grounds for caution. Paradigm shifts have happened in psychiatry. A clinical trial that would span many years, would be resource intensive, and would be technically difficult seems especially vulnerable to disruption from a paradigm shift. It is not hard to imagine scientific advances that would initiate a paradigm shift in schizophrenia: effective preventative measures, biomarkers that distinguish different kinds of psychotic illnesses, predictors of antipsychotic response and non-response, pharmacotherapies with new mechanisms of action, targeted brain stimulation techniques, and agents with disease modifying potential are a few examples. Paradoxically, the more optimistic psychiatrists are about any of these breakthroughs happening soon, the more cautious they should be about embarking on a long, costly, and difficult clinical trial studying antipsychotic maintenance treatment.

The potential for a paradigm shift to diminish or truncate the benefits derived from these studies should be a consideration for researchers, funding agencies, and ethical review boards. In their essay, "What makes clinical research ethical?," Emanuel et al. list 7 requirements.⁴² Three of them—value, scientific validity, favorable risk-benefit ratio—are potentially paradigm specific and subject to change when a paradigm shift occurs. While researchers, funders, and ethical review boards cannot be expected to forecast paradigm shifts with specificity, or to predict the future state, it would be reasonable to ask them to identify and remain cognizant of "anomalies" (Kuhn's term for observations not easily reconciled with the paradigm) or areas with high potential for change or disruption. The potential for paradigm shift could then be explicitly considered as projects examining these areas are designed and reviewed.

The position taken in this essay, which is both cautious and optimistic, has limitations that require several acknowledgements. The current paradigm remains alive and well and it is likely that meaningful discoveries will still be made within this paradigm. When paradigms shift, there are elements of continuity that persist, such that not everything is discarded with the old paradigm (although predicting what will translate into the new paradigm and what place it will hold can be difficult). Perpetually

waiting for paradigms to shift before embarking on research initiatives would greatly limit discovery within the current paradigm, and would halt the process of evolving toward the next paradigm. Concerns for a paradigm shift might appear misplaced in hindsight if new developments take many years or decades to materialize; meanwhile, patients and clinicians rely on suboptimal evidence to make important treatment decisions.

Conclusion

There is no question that psychiatry would benefit from successful long-term, double-blind, randomized, placebo-controlled trials to inform clinical decisions about how long to continue antipsychotic medication. The question is how long the benefits would endure, and whether the benefits would justify the costs and risks associated with such trials. Paradigm shifts in schizophrenia have occurred, changing both the questions and the answers that people care about. While it would not be wrong to move forward with considering these trials, stakeholders should remain aware that data generated today may not be as meaningful tomorrow. In weighing all of the considerations mentioned above, it seems unlikely that the benefits will be worth the investment.

Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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