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# Rationale and Parameters for Medication-Free Research in Psychosis

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Bola (this issue) makes a case for off-medication periods being relatively safe in schizophrenia, at least in some circumstances. What are the implications of this for research and for the clinical care of research participants?

In 1977 Carpenter, Strauss, and I argued that a place should remain in psychosis research for medication-free investigation.[1] Our ultimate rationale for this position was that "we know virtually nothing about the etiology of schizophrenia."[1p14] Today I maintain that our ignorance remains as profound as it was 29 years ago and that unraveling the mysteries of schizophrenia still requires observing it under natural conditions, ie, without antipsychotic medications. On the other hand, medication has revolutionized the treatment of psychosis, and it is absolutely required under certain circumstances. My comments here will touch upon both elements of this conundrum and will address the conditions under which the dual aims of scientific clarity and patient safety can be realized.

## The Case Against Medication

Antipsychotics obscure the pathophysiology of psychosis by altering the neurobiology of the brain and the natural history of disorder. Dopamine D2 receptor blockade is the final common path to chemical antipsychotic activity.[2] The dopamine system underlies reward prediction and motivational salience.[3] When overactive, it aberrantly assigns importance to specific experiences, which results in positive symptoms. When underactive, it attenuates motivational salience for all events, which results in negative symptoms. In the short term, acute D2 blockade detaches salience and the patient's investment in positive symptoms. In the long term, chronic D2 blockade dampens salience for all events in everyday life, inducing a chemical anhedonia that is sometimes labeled postpsychotic depression[4,5] or neuroleptic dysphoria.[6–11]

Maintenance medication with chronic D2 blockade may also induce changes in the natural history of the patient's disorder. We postulated 29 years ago[1] that initial exposure to antipsychotics may actually increase the risk of relapse but that, like tardive dyskinesia, this risk could be masked by continuing medication. Without question medication and relapse are related,[12] and today that relationship has come to mean medication is required to prevent relapse. What we asked in 1977 was whether the actual risk for relapse would be as high in samples that were never exposed to neuroleptics to begin with.

Clinical trials randomizing first-episode psychotic patients to a no-drug arm are not likely to happen in the foreseeable future, but the question about chemically induced relapse risk and chronic deficit may not be merely academic. The long-term (9- and 10-year) outcome data emerging from 2 well-treated, first-episode samples[13–15] suggest that deterioration in schizophrenia does not plateau as seen in older, long-term follow-up patient samples where exposure to medications was absent or intermittent.[16–19] Could it be that the drug-related chronic deficits in motivational salience for experience lead to a form of extra-institutional institutionalization? Do we free patients from the asylum with D2 blocking agents only to block incentive, engagement with the world, and the joie de vivre of everyday life? Medication can be lifesaving in a crisis, but it may render the patient more psychosis-prone should it be stopped and more deficit-ridden should it be maintained.

## The Case for Medication

The benefits of medication are profound. Active psychosis is a dangerous, life-threatening state. Behavior is often unpredictable because of misperceptions, misconceptions, and irrational thinking. The gravest dangers are suicide, homicide, and physical injury. Almost as important are paralyses of judgment and empathy resulting in violations of social convention and trust and leading ultimately to social isolation and stigmatization. For persons in this state of mind, antipsychotic medications are unquestionably a powerful therapeutic tool. Furthermore, the efficacy of drugs for active psychosis is inexpensive compared with nondrug alternatives that would require varying degrees of hospital/institutional care. Drugs are also portable, unlike treatment teams, and facilitate rapid emancipation of the remitted patient to the community.

The benefits of medication are also obvious, almost as obvious today as they perhaps were to the astonished alienists in the 1950s who bore first witness to

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chlorpromazine's power to unravel the knots of psychosis. The therapeutic power of medication has been scientifically validated countless times since then, and it is now the primary treatment of schizophrenia. In today's climate, treating schizophrenia without medication mobilizes high anxiety among treaters for the safety of their patients from irrationality and for the safety of themselves from litigation.

## The Case for Periods of Medication-Free Research in Psychosis

Antipsychotics alter the pathophysiology and the natural history of schizophrenia. At the same time, they are the most rapid, effective, and economical treatment for active psychosis. How do we resolve this tension? Two approaches are offered, one focusing on pre-onset detection of high-risk cases and the other on creating safe conditions for the drug-free study of active and remitted states in established psychosis.

Early detection and intervention in the prodromal phase of first psychosis offers the potential for therapeutic advance in the form of preventing onset and/or progression of disorder.[20–22] The major scientific promise of early detection, however, is the opportunity to study the pathophysiology of psychosis medication-free. True-positive high-risk cases can now be reliably identified and monitored prospectively to the onset of psychosis.[23] This offers 2 advances in scientific design. First, it makes possible the prospective tracking of changes leading to psychosis, as opposed to retrospective reconstructions of those changes, which ultimately remain speculative and nonfalsifiable. Second, this tracking can be done free of medication because clinically there is not yet any dangerous loss of reality testing and/or behavioral control and because medicolegally there is not yet any DSM diagnosis of psychosis.

This approach demands active, frequent, and careful monitoring of "prodromal" cases. If the considerable psychosocial resources required for such monitoring cannot be offered by the clinical research team, then the research should not proceed.

Medication-free research could also be engineered for established schizophrenia, for patients either actively psychotic or in remission, if an equivalent level of safety could be established, as in the case of prodromal schizophrenia. For established psychosis, this requires the availability of even more psychosocial resources than the "prodromal" situation. Medication-free *active* psychosis, for example, can only be studied in the context of 24-hour hospitalization *with* constant observation. Medication-free remitted psychosis can only be studied in the context of the patient consenting to a contract to undergo regular monitoring and to comply with a recommendation for the institution or reinstitution of medication by the monitoring team.

Both of these scenarios for the established patient can be created but are problematic scientifically and economically. Scientifically, the samples of patients consenting to such research conditions are likely to be less severely ill and therefore not representative of the larger population of persons with psychosis. Economically, such resources required for safety simply do not exist, at least in the American managed health care system. Such resources would have to be part of the direct costs of research grants. Up to now, National Institutes of Health policy has proscribed any culture of providing clinical treatment infrastructure that supports research addressing questions other than the efficacy of the clinical treatment infrastructure under investigation. Unless and until that policy can be successfully challenged and altered, medication-free research in psychosis will be possible only in the "prodromal" situation. Given this, the time may be near to generate such policy challenges.

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