EDITORIAL

# Antipsychotic Medication During the Critical Period Following Remission From First-Episode Psychosis
## Less Is More

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*If you come to a fork in the road, take it.*
**Yogi Berra**

**The person recovering from** a first episode of psychosis (FEP), the family, and the treating clinical team have until now faced a real dilemma. Having reached the base camp of remission of psychotic symptoms, how long should antipsychotic medication be continued? Most guidelines propose a trial of dose reduction and discontinuation, all being well, after 12 months of treatment with careful monitoring subsequently. However, it is only recently that studies have been carried out to derive evidence regarding this decision.

In the early 21st century, the goal of treatment in FEP must be to pursue as full a functional recovery as possible. This means a meaningful life with vocational recovery, positive relationships, social inclusion, and good physical health. The worldwide development of specialized early psychosis care is based on these goals. As with cancer, and chronic disease generally, early detection and sophisticated use of the existing therapeutic armamentarium, even without dramatic breakthroughs, can not only save and extend lives but also facilitate many more recoveries. The "soft bigotry of low expectations" in psychosis is under serious challenge. Many would now contend that much of the poor outcome in psychosis is an artifact of late detection, crude and reactive pharmacotherapy, sparse psychosocial care, and social neglect. Despite 60 years of use of antipsychotic medications, it is only now becoming clearer how best to use these medications to maximize recovery.

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A key issue in the management of FEP is relapse prevention in the early years after diagnosis when relapse rates are known to peak. Clinicians understandably want to safeguard a hard-won remission, influenced by the fact that the strongest predictor of relapse is medication nonadherence (relative risk, 4) (although there are several other environmental risk factors, notably, substance misuse and family climate[1]). Furthermore, discontinuation studies have shown increased relapse rates in patients who discontinue drug therapy, approaching 80% to 100% within 5 years in mainstream psychiatric care (nonspecialized for FEP) if sensitive positive symptom-based definitions of relapse are used.[2-4]

Relapse has been variously defined from simply readmission to a hospital at one extreme to temporary exacerbation of positive symptoms with minimal functional impact at the other extreme. The former is too insensitive, but the latter might be too sensitive to serve as a basis for treatment decisions. Until now it has been assumed that relapse prevention is the top priority in treatment and a prerequisite for functional recovery, since genuine relapses are risky and distressing, setting back recovery in all domains. Although relapses were appropriately seen as a genuine threat to recovery, all too often, in research and clinical practice, prevention of relapse became an end in itself rather than an intermediate goal on the path to recovery.

The data reported by Wunderink et al[5] highlight these issues and pose a challenge to linear thinking in relationship to relapse. They appear to put relapse in perspective. Although certainly not desirable, a contained relapse is rarely the end of the world. Modest exacerbations of symptoms, which are more common in the 3 to 5 years after diagnosis, may be a price worth paying for better longer-term functional recovery. A trade-off may be available.

Wunderink and colleagues[5] randomized 128 patients with remission of psychosis to dose reduction/discontinuation (DR) or maintenance treatment (MT) for 18 months. At 18 months, there had been twice the rate of relapse in the DR group (43% vs 21%)[6] yet no more than a trend for better functional outcomes, consistent with both conventional wisdom and other recent data showing discontinuation to be an unwise course even in patients with remission.[2] However, at 7 years' follow-up by Wunderink et al, the picture had changed dramatically. Patients assigned to DR manifested no increased relapse rates (the excess was confined to the first 3 years) yet achieved twice the level of functional recovery (40.4% vs 17.6%). Random assignment to DR had in fact resulted in minimal or very low-dose use of antipsychotic medications more frequently than did MT. That this was done randomly means that the 7-year results are very unlikely to be confounded. Ultimately, this study demonstrates that with antipsychotic medication in the critical period of FEP, "less is more."

### Dosing in FEP and Antipsychotic Load

We are still learning and relearning about correct dosing with antipsychotic medications. It has long been known that the dose of antipsychotic medication required to produce remission, particularly in FEP, was very low and closely linked to the dose that produced extrapyramidal symptoms (the neuroleptic threshold).[7,8] Positron emission tomography studies

later teased apart these thresholds, confirming the notion that low doses of antipsychotic medication were both sufficient and optimal, especially in patients with FEP.[9] Unfortunately, in routine clinical practice the secondary distress and behavioral disturbances associated with delayed treatment of acute psychosis are often managed with antipsychotic medications rather than psychosocially or with benzodiazepines. Consequently, the neuroleptic threshold is usually exceeded in FEP with subjectively aversive impact and unnecessary adverse effects. The same argument may now be applicable to the recovery phase, in which it seems that if the antipsychotic load (similar to neuroleptic threshold) is minimized to a very low-dose level, functional outcomes are better. One explanation for this finding flows from understanding the effects of excessive dopamine blockade, which saps initiative and drive and compromises key cognitive processes. Combined with weight gain and loss of confidence, the sensitive functional recovery path is likely to be seriously blocked. Subtle rebalancing of the dopamine system should be the pharmacologic goal. In nonresponders to dopamine-blocking medications, dopamine hyperactivity may not prove to be the primary target. In addition to lowering the antipsychotic load, an early guided discontinuation strategy would find the small subset of patients who can recover with no antipsychotic medications—those whose first psychotic episode will also prove to be their last.

## Synergistic Role of Psychosocial Interventions in Maximizing Recovery

Reducing antipsychotic load may be one strategy to promote recovery; however, in the Wunderink et al[5] study, functional recovery occurred in only 40% of the participants. Contributing factors to this finding may be that the study occurred in a standard adult psychiatry service and that intensive specialized early psychosocial interventions were not available. We now know that early functional recovery predicts full functional recovery at 8 years better than does clinical remission.[10] Strategies targeted at maximizing early functional recovery, notably, vocational programs,[11] could be complementary and potent, significantly increasing recovery rates. Synergies may be found with the DR strategies pursued in the Wunderink et al project. The cost might be somewhat elevated rates of symptomatic relapse; however, this could also be preventable. We also know that psychosocial relapse prevention strategies can greatly reduce relapse rates, at least during the intervention period, following remission from FEP.[12] Although the rates rise again when the intervention is withdrawn, innovative online interventions are being developed to create longer-term protection and a "soft landing."[13]

## Conclusions

It now seems probable for patients who achieve clinical remission from FEP that as many as 40% can achieve a good long-term recovery with use of no or low-dose antipsychotic medication. It is important to identify these patients at an early stage. Combining DR strategies with proactive psychosocial recovery interventions maximizing early functional recovery, delivered in specialized, optimistic systems of early psychosis care, is likely to further increase the percentage of full functional recovery. Physical health would also be expected to improve through reduction of antipsychotic load and greater levels of social inclusion and employment.

The crude use of antipsychotic medications, the delay in building evidence to guide their use, the ideological storms that continue to distort the discussion, and the tendency of human beings to seek either/or solutions to problems have combined to cause us to pose the wrong questions. In moving to a more personalized or stratified medicine, we first need to identify the probably very small number of patients who may be able to recover from FEP with intensive psychosocial interventions alone.[14] For everyone else, we need to determine which medication, for how long, in what minimal dose, and what range of intensive psychosocial interventions will be needed to help them get well, stay well, and lead fulfilling and productive lives. These factors have rarely been the goal in the real world of clinical psychiatry—something we must finally address now that we are armed with stronger evidence to counter poor practice. Antipsychotic load is a key concept that takes us beyond polarized views stoked by alarmists on the one hand and hard neurobiological reductionists on the other.

What are the next steps? A more complex trial of DR augmented by a suite of relapse prevention and early functional/vocational recovery interventions buttressed by online strategies over the first 5 years after diagnosis is now required. Such research needs to be complemented by the search for safer medications, by the safer use of existing medications, and by a proactive focus to identify and fast-track to clozapine and intensive psychosocial care those patients who fail to get to the first base of early remission. These studies, which require a multicenter design for adequate sample size and power, will be increasingly feasible as networks of specialized early psychosis programs continue to expand across the developed world.


### ARTICLE INFORMATION

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