The debate regarding maintenance treatment with antipsychotic drugs in schizophrenia

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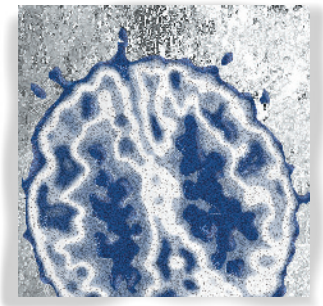

Introduction

Serendipitous observations and research conducted between the 1950s and the 1970s provided uncontroversial evidence that drugs which block dopamine (DA) receptors ameliorate acute agitation, delusion, hallucination, and thought disorder, all characteristics of the schizophrenic illness.[1] Because the natural course of schizophrenia is characterized by alternating periods of psychotic symptom emergence, improvement, and re-emergence, researchers in the 1970s and 1980s investigated the possibility that the same DA-blocking drugs might also reduce the risk of symptom re-emergence.[2]

Several large meta-analyses of maintenance trials have confirmed that patients who suffer from chronic schizophrenia, randomized to placebo, are likely to experience earlier symptomatic worsening than patients randomized to a dopamine (DA)-blocking drug. These findings led expert groups to issue treatment guidelines, which recommend treatment with DA-blocking drugs for periods ranging from several years to indefinitely. The recommendations were accepted by the majority of, but not all, the experts, some of whom proposed a targeted or intermittent therapy approach by which DA-blocking drugs are discontinued upon symptomatic remission, to be renewed in case of symptom re-emergence.
The debate between continued and targeted treatment approaches arises from disagreements regarding scientific and ethical questions. Scientifically, the discussion focuses on the quality and interpretation of the supporting or detracting evidence regarding each treatment option. For example, what is the percentage of individuals who can maintain stability off drugs? What is the rate of individuals who exacerbate despite maintenance treatment? What is the percentage of individuals who experience drug-related adverse effects? How can we interpret results of open-label, nonrandomized targeted trials? Regarding ethical questions, the debating sides disagree on how to weigh the impact of the decreased risk for exacerbation versus the certainty of adverse effects on the patient's quality of life, and how to reach a patient-therapist shared decision within the constraints of mental illness.

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The fact that the same drug might ameliorate symptoms during a disease flare-up can also reduce the risk of future flare-ups is well-documented in medicine: for instance, steroids ameliorate flare-ups and of rheumatoid arthritis and reduce the risk of future flare-ups.[3]

A comprehensive meta-analysis of placebo-controlled maintenance trials has confirmed that patients randomized to placebo are likely to experience earlier symptomatic worsening compared to patients randomized to a DA-blocking drug.[4] These findings have led professional organizations and expert groups to issue treatment guidelines recommending that individuals who manifest acute psychosis and meet diagnostic criteria for schizophrenia should be treated with DA blocking drugs for 1 to 3 years after symptom reduction or remission.[5] Despite some variability between guidelines, it is also recommended that individuals who experience symptom recurrence should continue treatment for many years to indefinitely.[6-8] The recommendations regarding the treatment of the acute phase of the schizophrenic illness are almost beyond debate. However, those regarding continuous maintenance treatment have been adopted by most researchers and clinicians[10] but questioned by others.[11-15] The latter proposes a targeted therapy approach by which DA-blocking drugs are discontinued upon symptomatic remission and renewed only in case of symptoms re-emergence.

Despite some reservations,[16] the case for continuous maintenance treatment is straightforward in that the risk for symptoms re-emergence persists long after resolutions of the acute symptoms. The argument recurring in several comprehensive reviews[9,10,17] is that the short- and long-term impact of exacerbations and hospitalizations on the patients' well-being justifies the immediate and cumulative adverse effects of the drugs. Since there are no diagnostic markers that distinguish between individuals who can maintain very long periods of symptom stability or remission in the absence of DA blocking drugs and those who would experience exacerbation,[18] and since the impact of exacerbation is harmful and demoralizing, all individuals affected by chronic schizophrenia should be encouraged to accept continuous, long-term maintenance treatment.

The case for the targeted treatment approach argues that, like almost all medical interventions, maintenance treatment has immediate and accumulating adverse effects; therefore, its use should be restricted to the minimum regarding dose and duration. Specifically, acutely ill patients should be treated until stabilized, after which the dose of medication should be reduced and subsequently discontinued. Should acute symptoms reemerge, the same cycle and procedure are to be repeated. Several follow-up studies supporting this approach have indicated that schizophrenic patients on a targeted treatment have better long-term outcomes, in terms of social and vocational performance than those on continuous treatment.[19-27]

The debate between continued and targeted treatment approaches arises from disagreements regarding scientific and ethical questions.[28] Scientifically, the debate focuses on the quality and interpretation of the supporting and detracting evidence regarding each treatment option. For example, what is the percentage of individuals who can maintain stability off drugs? What is the percentage of individuals who exacerbate despite maintenance treatment? What is the percentage of individuals who experience different drug-related adverse effects? What is the clinical significance if any, of brain volume loss? How to interpret results of targeted trials, most of which are open-label, non-randomized trials? On the ethical aspect, the debating sides disagree on how to weight the impact of the decreased risk for exacerbation versus the certainty of mild-to-moderate AE and the risk of severe AE on the patient's quality of life.[29]

Critique and defence of the continuous maintenance approach

Dopamine sensitization

Continued blockage of DA receptors may cause receptor super-sensitivity, which might, upon abrupt discontinuation of antipsychotics, contribute to rapid and frequent exacerbation.[11,30] This idea is supported by studies in rodents demonstrating that chronic treatment with antipsychotics increases DA receptor densities.[31] It is argued, the worsening of symptoms upon discontinuation of antipsychotics might reflect the effect of withdrawal rather than loss of the benefit of the drugs.[32] An alternative explanation for rapid worsening upon drug discontinuation is the possibility that antipsychotic drugs with intrinsic anticholinergic effects produce cholinergic rebound upon discontinuation, which manifests as general malaise and can be mistaken for symptom worsening.[33] However, a meta-analysis that looked at trials comparing

abrupt versus gradual discontinuation of DA-blocking drugs found no differences between the two modalities regarding symptom worsening.[4] Recent publication supports this assertion, showing that most relapses occur months and years after discontinuation rather than upon or immediately after discontinuation.[34]

Brain volume loss

Meta-analyses of imaging studies have demonstrated a correlation between cumulative exposure to antipsychotics and gray-matter loss,[35-37] which in turn might be responsible for the cognitive[38] and social impairments[39] observed in schizophrenia. Still, loss of brain tissue has been reported in premorbid and first-episode patients who were drug-naïve or had received antipsychotics only for brief periods of time. An alternative explanation posits that larger cumulative doses of antipsychotics could reflect a more severe form of illness, which could be associated with tissue loss. However, at least one study indicates that the correlation between cumulative exposure to antipsychotics and tissue loss is maintained even when controlling for severity of illness.[40]

Premature death, metabolic abnormalities, and cardiovascular morbidity

It is well-established that schizophrenic patients die earlier than age-matched controls,[41] and that antipsychotics drugs increase risk for diabetes, abnormal blood lipids, and weight gain, which in turn increase risk for cardiovascular disease and death.[10,42,43] However, other reasons, such as poor access to medical care and suicide, might contribute to premature death. Furthermore, data indicate that compliance with antipsychotic medication might reduce death rate. [34,44] One explanation for such discrepant findings is that the reduced rate of death associated with compliance to antipsychotic treatment reflects a general tendency to be compliant with medical treatment and a healthier life style, rather than a direct benefit of antipsychotic drugs.

Lack of ecological validity and other methodological limitations

Most maintenance placebo-controlled trials last between 6 and 12 months,[16] which might be too short for an illness with a lifetime course to be informative. Also, events such as violent outbursts or even hospitalizations, used as outcomes in maintenance trials, are not necessarily surrogates for illness worsening and exacerbation but could reflect the reaction of society to any aberrant behavior in an individual with a diagnosis of schizophrenia. Furthermore, maintenance trials comparing a DA-blocking agent with placebo cannot be truly blinded since the drugs have AE that are known and anticipated by both patient and the investigator/rater,[45] which biases the results in favor of the active drug over placebo.

Poor tolerability affecting patient's quality of life

Antipsychotics differ regarding tolerability profile, and individual patients experience each adverse effect differently, but none is devoid of tolerability problems. Akathisia, stiffness, tremor, apathy, sedation, lethargy, avolition, slowness of movement, and weight gain are AE which affect a patient's daily life.[46] Furthermore, since some of the AE are visible to others, it might amplify the stigma associated with the illness.[47] Using the minimal effective dose and supplementing with anticholinergic drugs might mitigate a few but not most of the AE.

Limited effectiveness

DA-blocking drugs, initially known as major tranquilizers,[48] are effective mainly for acute agitated behavior and some aspects of psychosis, while the phenomenology of schizophrenia includes negative symptoms, impairment in judgment, and cognitive and social functioning, impairments on which the DA-blocking drugs have no direct therapeutic effect.[49] On the contrary, they may even produce secondary negative symptoms in addition to the intrinsic primary negative symptoms.[50,51] Indeed, patients followed for a very long time off antipsychotics have less negative symptoms compared to treated patients.[52] Since DA neurotransmission mediates brain reward circuits,[53-55] it can be hypothesized that blocking DA receptors might deprive patients of experiences of pleasure and expecting reward(s).

Furthermore, questions have been raised as to whether improvements on psychometric scales, while being sufficient to demonstrate statistically signifi-

cant differences between drug and placebo, are also clinically meaningful.[56-59] Even if the advantages are clinically meaningful, it is not obvious whether maintenance treatment has a real impact on the social and vocational reintegration of patients, most of who remain socially isolated and unemployed.[60] Moreover, the beneficial effects of antipsychotics seem to decrease as a function of study duration.[4] Proponents of the continuous treatment hypothesized that the biological effect of the drugs remains unchanged, but as the trial continues, compliance with treatment decreases, nullifying the advantage of being in the active arm versus the placebo.[10]

It is also accepted that several biologically distinct abnormalities probably coexist under the diagnostic umbrella of schizophrenia,[61-63] making it improbable that the same pharmacological intervention–interference with the DA neurotransmission–would be effective for all subgroups. In maintenance trials at least 20% of the patients randomized to the active drug have the same time course in terms of symptoms as those randomized to placebo,[4] and antipsychotics appear to lose efficacy after 5 to 10 years of treatment in about two-thirds of the treated patients.[64] Between patients who can maintain remission without need for antipsychotics and patients who are actively psychotic despite antipsychotic treatment or treatment-resistant,[63] it seems that a considerable number of patients are subjected to the adverse effects of antipsychotics without clear benefit.

Critique and defense of the targeted treatment approach

Risk of exacerbation

Trials comparing early versus late discontinuation of antipsychotic drugs in first-episode patients demonstrated higher exacerbation and hospitalization rate in the former group.[34,65] Controlled trials comparing targeted versus continued maintenance treatment in chronically ill patients reported more exacerbation and hospitalization in the targeted arm.[66] Furthermore, relapses may impact the long-term outcome negatively as symptoms may not return to pre-discontinuation baseline.[67] However, contrary evidence also exists, indicating that when antipsychotics are reinstated, symptoms return to baseline.[68,69]

Selection bias and reverse causality

Trials that demonstrated better outcome(s) after several decades of follow-up of patients receiving targeted or no maintenance treatment at all did not use a random assignment design[70] or utilized old, inadequate methodologies,[71] and the results were affected by attrition bias.[72] Patients with less severe symptoms at baseline might have been selected for follow-up when off drugs, while patients with a more severe illness at baseline were followed up when on drugs.[73,74] However, even if that has been the case, it still demonstrates that a subgroup of above 20% of patients with a diagnosis of schizophrenia does not experience psychotic symptoms in the absence of antipsychotic drugs.[75] Furthermore, at least one study demonstrating the advantages of targeted therapy used a random assignment design.[76]

The ethical dilemma

Having seen repeated exacerbations, patients' anguish, hospitalization, and socially unacceptable behaviors of patients who discontinue medications, most psychiatrists and mental health workers concur with the guidelines and advise patients and their families to adhere to continuous maintenance treatment.[77] However, a very high percentage of patients discontinue medications against medical advice.[78] Others titrate their own medications to avoid AE, or take medications only when they believe their symptoms are getting worse. Some patients insist that medication discontinuation be attempted, despite concurring with medical advice. Since impaired judgment characterizes schizophrenia, the patients' negative attitude towards medication might be attributed to poor insight into the illness and the benefits of medication.[79,80] This view, although not devoid of scientific support,[81] aligns poorly with notions of respect for patients' autonomy[82,83] and shared decision-making.[84,85] To complicate matters even more, it is also conceivable that some patients who do not adhere to their prescribed treatment are making informed decisions that the increased risk of symptom worsening is preferable to the certainty of adverse effects.[86] Such decisions are supported by the existence of subgroups of patients who would maintain symptom stability and would better function socially and vocationally when off antipsychotic drugs.[87] Regardless of the final decision if to stay on medication or not, physi-

cians have the duty to protect patients from making bad treatment decisions.[88]

Although results of well-conducted trials are the foundation of clinical decision making, physicians' psychological biases might also play a role. The recent memory of the last patient who has discontinued treatment, exacerbated, and "got into trouble"(ie, availability bias) [89] probably affects treatment decisions more than the patients who were lost to follow-up and were doing well without any treatment.[90] Likewise, negative outcomes, such as risk for exacerbation, hospitalization, or aberrant behavior are given more weight in medical decisions than positive outcome, such as the certainty of living without the AE of drugs (ie, negativity bias).[91] While the main priority for a treating psychiatrist is to avoid symptom exacerbation and hospitalization, for a patient it might be looking slim and avoiding stiffness.[11]

Conclusion

In summary, despite the benefits of DA-blocking drugs for some aspects of schizophrenia, available data have not provided satisfactory answers to the dilemma raised by maintenance treatment,[92] for the practising clinician who treats patients with residual and/or negative symptoms or who are reluctant to accept the adverse effects of DA blocking drugs (see World Psychiatry Forum 2018). Future research will have to address these questions: (a) what should be the criteria for the selection of candidates for discontinuation of maintenance treatment? (b) how can we ascertain that the patient indeed understands the risk and benefits of treatment discontinuation? (c) once discontinued, how can we distinguish, in a "vulnerable" individual, between normal reaction to daily life stresses and impending symptom exacerbation requiring re-instatement of treatment, or what should be the threshold for reinstating treatment? (d) are any of the suggested protective factors such as abrupt onset, female gender,[93] or biological markers[94] clinically useful? (e) and, is past experience of early[95] and protracted stability, or of rapid exacerbation, predictive of the same in the future? [93]

Hopefully, current research will produce better-tolerated drugs for schizophrenia, targeting negative symptoms[96] and cognitive impairment, which do not necessarily block DA receptors[97-99] hence, devoid of the associated adverse effects. ❑

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