What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia?

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The long-term benefit-to-risk ratio of sustained antipsychotic treatment for schizophrenia has recently been questioned. In this paper, we critically examine the literature on the long-term efficacy and effectiveness of this treatment. We also review the evidence on the undesired effects, the impact on physical morbidity and mortality, as well as the neurobiological correlates of chronic exposure to antipsychotics. Finally, we summarize factors that affect the risk-benefit ratio. There is consistent evidence supporting the efficacy of antipsychotics in the short term and mid term following stabilization of acute psychotic symptoms. There is insufficient evidence supporting the notion that this effect changes in the long term. Most, but not all, of the long-term cohort studies find a decrease in efficacy during chronic treatment with antipsychotics. However, these results are inconclusive, given the extensive risk of bias, including increasing non-adherence. On the other hand, long-term studies based on national registries, which have lower risk of bias, find an advantage in terms of effectiveness during sustained antipsychotic treatment. Sustained antipsychotic treatment has been also consistently associated with lower mortality in people with schizophrenia compared to no antipsychotic treatment. Nevertheless, chronic antipsychotic use is associated with metabolic disturbance and tardive dyskinesia. The latter is the clearest undesired clinical consequence of brain functioning as a potential result of chronic antipsychotic exposure, likely from dopaminergic hypersensitivity, without otherwise clear evidence of other irreversible neurobiological changes. Adjunctive psychosocial interventions seem critical for achieving recovery. However, overall, the current literature does not support the safe reduction of antipsychotic dosages by 50% or more in stabilized individuals receiving adjunctive psychosocial interventions. In conclusion, the critical appraisal of the literature indicates that, although chronic antipsychotic use can be associated with undesirable neurologic and metabolic side effects, the evidence supporting its long-term efficacy and effectiveness, including impact on life expectancy, outweighs the evidence against this practice, overall indicating a favorable benefit-to-risk ratio. However, the finding that a minority of individuals diagnosed initially with schizophrenia appear to be relapse free for long periods, despite absence of sustained antipsychotic treatment, calls for further research on patient-level predictors of positive outcomes in people with an initial psychotic presentation.

Key words: Long-term antipsychotic treatment, schizophrenia, benefit-to-risk ratio, efficacy, effectiveness, physical morbidity, mortality, metabolic disturbance, tardive dyskinesia, psychosocial interventions, non-adherence, dopaminergic hypersensitivity

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Schizophrenia is a disorder characterized by acute episodes often followed by symptom improvement[1]. Most guidelines recommend at least 1-2 years of antipsychotic treatment after symptom remission of an acute episode[2-5]. Of those discontinuing antipsychotic treatment, up to 75% have a relapse within 12 to 18 months[6,7]. Meta-analyses of 26 to 52 week studies comparing second-generation antipsychotics vs. placebo in the prevention of relapse found a very favorable number-needed-to-treat (NNT) of 3-5[8,9].

Risks of acute antipsychotic treatment, compared with placebo, mostly include weight gain, metabolic disturbance, QTc prolongation, neurologic adverse effects and sedation[10]. It is generally accepted that, given the usually moderate magnitude of these potential side effects and the availability of strategies to manage them, as well as the efficacy of antipsychotics in preventing relapse, antipsychotics have a favorable risk-benefit balance during the first 1-2 years following an acute psychotic episode[2-5,11].

Clinical guidelines do not provide systematic recommendations for treatment continuation or discontinuation beyond 1-2 years, yet they warn about the risks of relapse associated with treatment discontinuation[2-5,11]. The effects of antipsychotic treatment beyond the first 2 years of treatment are not well understood, given the lack of double-blind, placebo-controlled randomized trials (RCTs)[9].

There has been an emerging body of literature on the long-term effects of antipsychotics questioning their necessity[12-15]. Long-term animal studies of antipsychotic exposure[16], naturalistic cohorts[14,15], and treatment discontinuation studies[13] have been cited by some authors who claim that antipsychotics do not improve outcomes in the long term, and that there may even be iatrogenic adverse consequences of long-term antipsychotic treatment[17]. Others suggest that there is insufficient evidence supporting iatrogenic effects[18]. Such debate, and the uncertainty in the interpretation of long-term studies, with inherent biases[12,19], results in unclear recommendations for clinicians.

In this paper, we review the literature on the potential risks and benefits of long-term antipsychotic treatment, summarizing the evidence of efficacy, effectiveness, tolerability, physical morbidity and mortality, as well as functional and structural brain changes associated with that treatment. Additionally, we review the role of interventions to optimize such risk-benefit ratio.

EFFICACY, EFFECTIVENESS AND TOLERABILITY

The longer the study, the more likely that systematic error accumulates over time and biases the results. Measurements tend to prioritize feasibility over reliability; the intervention is less controlled due to

greater influence of environmental factors; and there is greater chance of systematic or non-random drop-outs differing between the arms of the trial.

Hence, the interpretation of the results should consider how each one of these potential biases affects the study. Interpretation should also consider the literature, not isolated studies. Here, we summarize the available data separately for different methodological approaches, as all have their own strengths and limitations[20-22].

Treatment adherence and long-acting injectable antipsychotic studies

The longer the treatment, the greater the chance of insufficient adherence[9,23,24]. Data from administrative claims in the US suggest that, in clinical practice, patients with psychosis treated in an outpatient setting fill their prescriptions an average of 40-60% of the days prescribed[25]. Adherence studies find that poor mid-term adherence ranges from 11.6% based on self-report to 58.4% in studies using serum concentration[23]. In addition to high rates of insufficient adherence[24], we lack practical/reliable measures of exposure[26].

In a systematic review and meta-analysis of longitudinal studies examining relapse and its risk factors in patients following stabilization after a first psychotic episode, non-adherence was found to be the greatest predictor of relapse among twenty variables in seven long-term studies, increasing the chance of relapse by 400%[27]. Individuals in another study with non-adherence for >1 month of an 18-month follow-up had a five-fold greater chance of relapse than individuals with continuous treatment[28].

Poor adherence was also found to explain up to 36% of the effect of cannabis on the number of relapses[29]. Individuals with suboptimal adherence were found to have greater body mass index and were less likely to live in independent housing than individuals with continuous adherence over 18 months. The magnitude of these risk factors was small to moderate, with a 2% greater likelihood of being non-adherent for each point of increase in body mass index, and a 25% greater likelihood of being adherent in individuals living independently. In this study, no other undesired outcomes were associated with adherence status[30].

Long-acting injectable (LAI) formulations have also provided meaningful data. When LAIs and oral formulations were compared in RCTs, no overall difference was found regarding relapse prevention in the mid term after stabilization[31]. This is not surprising, given that the control groups taking oral medication in these RCTs tend to include patients with better treatment adherence and lower illness severity. Non-adherence levels did not differ across ten meta-analyzed trials with adherence data ($p=0.27$)[31].

When the same question was addressed by meta-analyzing mirror-image studies, where each research participant acts as his/her own control, LAI treatment phases, compared to those with oral antipsychotics, were associated with a significantly 57% lower risk of a next hospitalization and a 62% reduced risk of number of hospitalizations[32]. This is not simply the result of the order of the oral and LAI phases, as two trials confirmed that the reverse switch (i.e. from an LAI to an oral antipsychotic) was associated with poorer outcomes for the oral phase[33,34].

The finding of greater effectiveness of LAIs in mirror image studies was replicated in a meta-analysis of cohort studies, where the number of hospitalizations was reduced by 15% (14 studies; 60,260 person-years), despite greater illness severity in the LAI cohorts than the oral antipsychotic treatment cohorts ($p=0.014$)[35]. Results were particularly apparent in Scandinavian registries, that have fully generalizable national samples. In a Finnish national cohort, individuals treated naturalistically with LAIs after their first hospitalization for a schizophrenia episode had one third the risk of re-hospitalization than individuals on oral counterparts of the same antipsychotics[36]. This was replicated in a Swedish cohort including all phases of illness, following patients for a median of 6.9 years. Six of the top eight antipsychotic monotherapies that were significantly superior regarding hospitalization risk compared to not receiving any antipsychotic (hazard ratios, HRs=0.51-0.64) were LAIs (with the two oral antipsychotics being clozapine and olanzapine)[37].

In a meta-analysis that compared adverse effects with LAIs vs. the same oral antipsychotics across sixteen RCTs with a mean duration of one year, those preparations did not differ regarding 115 (96.6%) of the 119 reported adverse effects[38]. LAIs were more likely to present with akinesia, low-density lipoprotein cholesterol change and anxiety, whereas oral antipsychotics were associated with greater hyperprolactinemia. Furthermore, there were no differences regarding treatment discontinuation due to side effects and mortality[38]. Little is known, however, about differences in adverse events beyond one year of treatment.

Overall, assuming that the main advantage of LAI over oral antipsychotics is lower risk of non-adherence, this literature supports the relationship between suboptimal adherence in the long term and greater risk of relapse[27,39], while differences in adverse effects are small within the time span of one year.

Placebo-controlled antipsychotic maintenance treatment studies

Methodologically, placebo-controlled maintenance RCTs have the advantage of minimizing systematic differences between groups, yet their time frame is only mid-term (i.e., 1-3 years following stabilization), and their results assume full long-term adherence with antipsychotics (which is known to decrease over time[24]). Increasing non-adherence even in RCTs could lead to finding lower effect sizes in studies of longer duration.

A meta-analysis of 65 placebo-controlled maintenance RCTs found an overall NNT of 3 favoring antipsychotics over placebo in preventing relapse, but overall treatment effects tended to decrease as a function of study duration[9]. The proportion of individuals unimproved/worse was lower on antipsychotics, but this

difference decreased over time and was non-significant in the longer-term studies.

Supporting the hypothesis that increasing non-adherence on antipsychotics could decrease antipsychotic maintenance efficacy, the authors found a significantly greater relapse preventive effect (p=0.03) in studies comparing LAIs vs. placebo (HR=0.31) than oral medications vs. placebo (HR=0.46). In LAI studies, non-adherence could be identified and non-adherent patients were discontinued or excluded from the analyses[9].

The number of patients with at least one adverse effect did not differ between antipsychotics and placebo, and did not increase over time for individuals on antipsychotics. No differences were observed in sedation, although weight gain and at least one movement disorder were significantly more frequent during antipsychotic treatment[9].

Long-term cohort studies

Few placebo-controlled RCTs of antipsychotics last >3 years, with most lasting ≤1 year[9]. Most data beyond this initial period are derived from non-randomized, non-controlled cohort and register studies. These have the advantage of providing long-term data, not requiring consent and being highly representative of the overall population. However, given the lack of randomization and controlled intervention, subgroups are subject to various types of selection biases, and conclusions are tentative.

Non-randomized cohort studies often found that, at follow-up, individuals on antipsychotics had equal or greater illness severity compared with those off antipsychotics. For example, in the Suffolk county cohort, 175 individuals with schizophrenia showed a clinical decline over the 20-year follow-up period[40]. This decline occurred despite high and constant rates of antipsychotic prescription (86.9% at baseline and 81.8% 20 years later), and antipsychotic use was associated with worse Global Assessment of Functioning (GAF) scores and negative symptoms, yet lower disorganization and excitement[40]. In the Chicago cohort, which followed 70 individuals with schizophrenia from early illness for 20 years, 8% of the 15 unmedicated individuals had some degree of psychotic symptoms, versus 68% of the 25 individuals treated continuously with antipsychotics[14]. In the Northern Finland 1966 Birth Cohort, which followed patients for almost 20 years, those who were off antipsychotics were more often in remission, and no differences in remission rates between treatment groups were found[41,42]. Similarly, the OPUS cohort in Denmark found that, among the 90% of the individuals who did not have sustained remission 10 years after their first episode, more were on than off antipsychotics[43,44].

Nevertheless, in those non-randomized, uncontrolled studies, adherence levels to antipsychotic treatment are unknown, and most importantly, there is a high risk of confounding by indication and reverse causation, in that greater illness severity could be the cause of continued antipsychotic treatment, rather than being the effect. Interestingly, different results were found in a retrospective cohort study of individuals with schizophrenia whose access to antipsychotic treatment had been restricted. In this cohort from rural China, those who had access to antipsychotics did substantially better after 14 years than those without access[45].

Thus, despite the pattern of patients with worse outcomes being overrepresented in the treatment groups of several cohort studies, the interpretation regarding cause and effect is difficult, and reverse causation cannot be excluded.

On the other hand, results from large, national samples analyzed with statistical methods to adjust for baseline differences support the notion that treatment failure and hospitalization[37], as well as mortality risk from suicide[46,47], are significantly greater in patients not receiving antipsychotics than in those who are.

Dose-reduction and dose-discontinuation studies

Dose-reduction and dose-discontinuation studies (DRDD) evaluate outcomes associated with these treatment strategies compared with long-term continuation of antipsychotic treatment. DRDD studies often have the advantage of a longer time span than antipsychotic maintenance trials, yet with greater degree of randomization and control than naturalistic cohort studies.

Wunderink et al[13] conducted the study with the longest follow-up period to date, consisting of two phases. In the first phase, 131 individuals with a first episode of psychosis were allocated to 2 years of either symptom guided DRDD or treatment continuation[48]. The initial goal of stopping antipsychotic treatment in the DRDD group was changed to dose reduction only, due to too many relapses after antipsychotic discontinuation. In the second phase, 103 individuals were evaluated once after 5 years of uncontrolled community treatment[13]. In the initial RCT, the DRDD group had twice as many relapses as the maintenance group (43% vs. 21%, p=0.011), although about 20% were able to successfully stop the medication without relapses. There were no differences in symptom severity, both groups having low Positive and Negative Syndrome Scale (PANSS) scores throughout[48]. At 5 years, there were no differences in relapse rates or symptom severity. However, recovery rates were twice as likely in the initial dose-reduction group (40.4% vs. 17.6%, p=0.004), driven not by symptomatic remission (69.2% vs. 66.7%, p=0.79), but by functional remission (46.2% vs. 19.6%, p=0.01), and 8 of the 11 patients off antipsychotics for 2 years were in the original dose-reduction condition. These results have been cited as important evidence that antipsychotics could postpone rather than prevent relapse, while impacting negatively on functional recovery in the long-term[12,14,15,17,19].

These findings should be interpreted with caution. As the authors acknowledge, the participants had very low symptom severity. Their conclusions might not apply to more severely ill patients. Also, the difference in antipsychotic exposure between the two groups was only questionably clinically meaningful (1.4 mg/day of haloperidol equivalents), without significant differences in months per

patient without antipsychotic prescription. Less than 50% of the sample approached for the original RCT agreed to participate, and only 43.7% of the patients at baseline were diagnosed with schizophrenia[48]. Therefore, it remains possible that the results were related to factors other than the 2-year intervention (i.e., DRDD or antipsychotic maintenance dose continuation), which was followed by 5 years of uncontrolled community care, especially given the small dose differences between treatment arms at 7 years. The lack of blinded assessment and reverse causation could also have influenced the results.

Antipsychotic dose reduction vs. standard maintenance dose has also been examined in other studies with shorter follow-up. In a meta-analysis of 13 trials with follow-up of 24 and 104 weeks (11 trials lasting $\geq$1 year), Uchida et al[49] found no differences between low antipsychotic dose (50-100% of the defined daily doses[50]) and standard antipsychotic dose, with respect to overall treatment failure (p=0.53) or hospitalization (p=0.40). Yet, very low dose (<50% of the defined daily doses[50]) were associated with greater risk of hospitalization (p=0.002) and relapse (p=0.0004). In a pilot study, cognitive symptoms were significantly improved when the antipsychotic dose was reduced to 50% of the defined daily dose[51].

A more recent uncontrolled discontinuation study with an intermediate follow-up period found greater rates of symptom recurrence and lower functional status in 46 individuals who had recovered from a single psychotic episode and who had opted to being treated with DRDD compared to 22 patients who had opted for continuation of antipsychotic treatment for 3 years[52].

Comments

There is a trade-off of strengths and weaknesses between study designs, with generally greater chance of bias in longer-term studies and, especially, uncontrolled studies in which more symptomatic and impaired patients are more likely to receive long-term antipsychotic treatment. There is consistent evidence, though, supporting the efficacy of antipsychotics in preventing relapse in the mid term (i.e., 1-3 years) following stabilization. These data come from studies of adherence, trials of LAIs, national registries, placebo-controlled maintenance trials and DRDD trials.

Most, but not all, of the studies with follow-up >3 years reported worse outcomes associated with continued antipsychotic use. However, these results are inconclusive, given small and selective patient samples and extensive risk of bias[13-15]. Conversely, long-term register studies of much larger and representative national cohorts of patients diagnosed with schizophrenia confirmed significantly less treatment failure and suicide-related mortality in antipsychotic-treated patients compared to those not treated with antipsychotics[37,46,47].

In conclusion, there is a strong evidence supporting mid-term efficacy, and a lack of convincing evidence against long-term efficacy of antipsychotic treatment.

PHYSICAL MORBIDITY AND MORTALITY

Schizophrenia is associated with a well-established excess of physical morbidity and premature mortality, while antipsychotics are associated with cardiovascular risk factors[53-60].

Individuals with schizophrenia have a greater prevalence of sedentary lifestyle, obesity, cardiovascular illness, diabetes, nicotine smoking and tobacco-related disorders, sexually transmitted diseases, obstetric complications, and altered pain sensitivity[61,62], while also having lower rates of health care services utilization and medical treatment for such conditions, which results in large unaddressed gaps in medical care[63]. While it is unclear the role that differences in health care systems play in physical morbidity in schizophrenia, given the limited availability of comparable data from a variety of countries[61], it seems clear that this morbidity plays an important role in reducing the life expectancy of individuals with schizophrenia across different settings.

A recent systematic review and meta-analysis including 11 studies from various countries found a weighted mean decrement in life expectancy of 14.5 years in patients with schizophrenia, with significant variations depending on gender and country[64]. While overall life expectancy has recently increased in developed countries, it is concerning that patients with schizophrenia appear not to have benefited from such improvements, so that the mortality gap affecting these patients has increased[65]. The drivers of this excess mortality seem to be poor physical health and decreased health care service utilization in patients with schizophrenia[66,67].

In the US, natural causes account for a vast majority of deaths, with only 1/7 related to unnatural causes (accidents, suicide or homicide). Chronic medical illness associated with smoking, obesity and a sedentary lifestyle account for most of the variance in premature mortality. These results seem to vary across countries, likely reflecting public health characteristics. A 10-year longitudinal study in Ethiopia found that premature mortality was double in patients with schizophrenia, with infectious diseases accounting for almost half of the causes of premature death, and with a greater role of suicide in premature mortality[68,69]. A similar pattern has been found in other developing countries[70,71].

The metabolic and cardiovascular side effects of long-term antipsychotic treatment have been a source of concern as possible contributors to the increase of physical morbidity and premature mortality, especially in developed countries where most of the mortality in schizophrenia is related to consequences of metabolic disturbance and cardiovascular disease[55,56,72]. While the metabolic consequences of long-term antipsychotic treatment are widely appreciated[53,54,57,58,60], the understanding of their contribution to morbidity and mortality in schizophrenia has evolved over the last several years.

There has been a growing literature identifying health care service utilization

patterns in schizophrenia associated with worse outcomes. In a national Swedish cohort, individuals with schizophrenia were less likely to have received a diagnosis of cancer or ischemic heart disease at the moment of dying of these causes[73]. These data suggest poor prevention and early treatment of medical conditions. In another sample, individuals with schizophrenia diagnosed with cardiovascular illness were less likely to use lipid-lowering and anti-hypertensive medication, which was altogether associated with worse outcomes[74]. To what extent antipsychotic treatment moderates the association between schizophrenia and poor health care utilization is not yet well understood.

The role of antipsychotics in reducing premature mortality in schizophrenia has been better characterized. Despite antipsychotic treatment elevating cardiovascular risk factors, long-term treatment is consistently associated with lower mortality rates compared to no long-term treatment[46,47,75-77], but still higher rates than in individuals without schizophrenia[46].

National registries constitute the best approach to study the relationship between long-term antipsychotic treatment and all-cause mortality as well as mortality related to cardiovascular illness, given the availability of cumulative dose data. In a seminal study, Tiihonen et al[47] found that, compared to individuals with schizophrenia not receiving antipsychotic treatment, those with longer antipsychotic treatment had greater decrements in premature mortality, including from cardiovascular causes[47]. Given the possible survivor bias, the same group studied the role of cumulative antipsychotic dose over a 5-year period in influencing mortality in schizophrenia adjusting for an extensive number of variables. They found in a separate sample that all – low, moderate and high – antipsychotic cumulative doses were associated with lower mortality rates than no antipsychotic use. Patients with schizophrenia with low and moderate – but not high – cumulative doses of antipsychotics had lower rates of mortality due to cardiovascular disease, whereas those with high – but not moderate or low – doses had low mortality rates due to suicide[46].

Beyond these individual findings, a recent meta-analysis found a consistent association of antipsychotic use and decrement in all-cause mortality, with some evidence of a dose effect[75]. The seeming disconnect between adverse antipsychotic cardiovascular effects in short- and longer-term studies and reduced (or, at least, not elevated) all-cause and cardiovascular illness-related mortality in long-term database studies may be explained by a beneficial link between improved psychiatric symptom control and improved healthy lifestyle behaviors as well as access to medical care[78].

Despite being consistent, these register-based findings should not be interpreted as clearly establishing a causal relationship between long-term antipsychotic treatment and reduced all-cause mortality, given the limitations of observational studies. However, national registries, despite their exposure to potentially unmeasured confounders, currently constitute the most adequate method to assess the long-term effects of antipsychotics on morbidity and mortality. Future research should improve their design by adjusting analyses for relevant potential confounders that have not been measured (e.g., body mass index, metabolic values, psychiatric illness symptom severity, and functionality).

Comments

Individuals with schizophrenia have significantly greater physical morbidity and premature mortality than the general population. While this finding is related to unhealthier lifestyle and lower health care service utilization, the role of antipsychotics is less clear. Long-term antipsychotic treatment is associated with significantly greater rates of metabolic and cardiovascular risk factors and disease, yet patients treated with antipsychotics over the long-term seem to have significantly lower mortality rates, including death due to cardiovascular disease, at low and moderate doses, compared to individuals with schizophrenia not receiving antipsychotics. This finding has been replicated with large effect sizes in various national registries, adjusting for an extensive number of potential confounders, and with some evidence suggesting a time and dose effect.

Though these data are limited by their observational nature, they are consistent enough to provide support for a favorable risk-benefit balance for the long-term use of antipsychotics in schizophrenia in reducing mortality.

BRAIN STRUCTURE AND FUNCTIONING

Schizophrenia has been associated with various brain volumetric abnormalities since the emergence of neuroimaging[79]. However, the nature and clinical relevance of these findings still remain unclear[80], and even less so the role of antipsychotics[18]. The cortical and subcortical regions found to have lower volume in schizophrenia have most frequently been the anterior cingulate cortex, insula, hippocampus, and thalamus[81,82], although several other areas have been implicated, with variability across studies probably due to methodological differences.

Never treated patients with chronic schizophrenia show a significantly accelerated decline in prefrontal and temporal cortical thickness[83], suggesting a neurodegenerative illness course. Reduced hippocampal and thalamic volumes have been observed in individuals at high risk of developing psychosis[84]. High-risk individuals who transitioned to psychosis presented with further progression of the whole brain volume reduction, even before antipsychotic treatment[85], and reductions in brain regions, such as the anterior cingulate, have been identified as potential biomarkers indicative of greater risk of transition to psychosis[86]. Despite grey matter reduction being a consistent finding, what this means at the neuropathological level is unclear[87-91].

Brain tissue loss is a non-specific finding, observed with antipsychotic exposure[92], changes in body weight[93], alcohol use[94,95], and steroid use[96]. Volumet-

ric changes in drug-naïve patients do not seem to be correlated with clinical impairment or duration of illness, not supporting a neurodegenerative hypothesis[83-86,97]. A more recent perspective is that volumetric reductions reflect a reduction of neuropil[80], and that volumetric variations can be heterogeneous in schizophrenia, although decrements in specific regions, such as the anterior cingulate cortex, might be more homogeneous and therefore more specific to that disorder[98].

A generalized decrement of grey matter volume associated with antipsychotic treatment duration and cumulative doses has been repeatedly reported[92,99]. However, these studies are limited by the fact that the duration and cumulative dose of antipsychotics can be a marker of illness severity or illness duration, making it difficult to distinguish a reduction due to illness severity, illness duration or antipsychotic exposure. In a meta-analysis of longitudinal studies, the grey matter decrement was directly related to the cumulative dose of first-generation antipsychotics during the window of observation, whereas the opposite was true for second-generation antipsychotics[97]. This finding is difficult to interpret and, as acknowledged by the authors, may in part be due to confounders, such as weight gain associated with second-generation antipsychotics.

Other findings contradict the notion that antipsychotics cause a decrement in grey matter in schizophrenia. The ENIGMA neuroimaging consortium found that, among 2,028 patients, antipsychotic-naïve individuals had greater volumetric deficits in the hippocampus compared with antipsychotic-treated ones[100], whereas thalamus and basal ganglia volume deficits in untreated patients have been found to be corrected with antipsychotic treatment[92,100]. A longitudinal study comparing grey matter volumes before and after initiation of antipsychotic treatment in first-episode patients found that antipsychotics minimized these decrements, particularly in the striatum[101]. Another study of patients who were stabilized on antipsychotic treatment and allocated to either antipsychotic maintenance or antipsychotic withdrawal found that after one year there were no differences in volumetric parameters between the two groups[102].

Brain volume reductions need to be interpreted within the context of the effects of untreated psychosis and of clinical outcome findings. The reanalysis of a study that had raised considerable concern about the potential dose-dependent adverse effect of antipsychotic treatment on brain tissue loss[103] revealed that the duration of psychosis had a 3-fold greater detrimental effect on total brain and frontal lobe grey matter loss compared to the duration of antipsychotic treatment[104]. Furthermore, brain volumetric changes do not seem to correlate with poor clinical response or outcomes. In patients treated with clozapine, both a grey matter decrement and a clinical improvement have been reported[105], whereas in other studies the opposite was found[106].

Moreover, measuring volumetric brain changes during antipsychotic treatment without assessing functional brain status confuses the discussion. A cross-sectional study in 23 antipsychotic-treated and 21 untreated first-episode patients found significant cortical thinning within the former group in the dorsolateral prefrontal and temporal cortex. However, the medicated patient group showed significantly higher dorsolateral prefrontal cortex activation and significantly better cognitive performance than the unmedicated group[107].

Thus, the evidence does not seem to support a causal or detrimental relationship between long-term antipsychotic use and clinically relevant brain volumetric changes, with some data even suggesting that brain volume reductions could be associated with better brain network integration.

Contrary to the ambiguous literature on structural changes with chronic treatment, findings on functional changes have been more consistent. Long-term antipsychotic treatment has been associated with an increase in the number and affinity of dopamine D2 receptors, which results in a state of dopaminergic supersensitivity, and has been replicated in animal[16,108] and human models[109]. Tardive dyskinesia is a clinical consequence of long-term antipsychotic use that has been associated with dopaminergic supersensitivity[110], but also other possible mechanisms[111], and with greater risk in genetically vulnerable populations[112].

The estimated risk of tardive dyskinesia with first-generation antipsychotics is 3-5% per year of exposure (at least for the first 5 years)[113], being lower with second-generation antipsychotics[114]. Early parkinsonism and higher antipsychotic doses have been associated with this side effect[115]. A recent meta-analysis estimated a global mean prevalence of 25% in patients with schizophrenia treated with antipsychotics, with great variability depending on geographical and treatment-related factors[115].

Some studies reported that patients with tardive dyskinesia are at greater risk of rebound psychosis upon antipsychotic withdrawal[116], development of treatment resistance[117], and physical morbidity and mortality[118], although these results have not been consistently replicated[119]. The degree to which chronic antipsychotic exposure plays a role in these potential outcomes associated with tardive dyskinesia (i.e., whether, beyond causing that side effect, chronic antipsychotic treatment has a causal role in these outcomes) is not well understood[120].

Second-generation antipsychotics should be first-line maintenance treatment agents to decrease the risk of tardive dyskinesia. Two agents, valbenazine and deutetrabenazine, have been recently approved in the US for the treatment of this side effect of antipsychotic treatment, having shown moderate to high efficacy[121,122].

Following the hypothesized mechanism underlying tardive dyskinesia, dopamine supersensitivity related psychosis either during antipsychotic treatment or upon antipsychotic discontinuation has been a theoretical concern[117,123]. The hypothesis is that chronic dopaminergic blockade resulting in dopamine D2 receptor upregulation and dopaminergic hypersensitivity in the mesolimbic pathway may increase the risk of relapse and reduce antipsychotic efficacy in the long term.

Dopamine supersensitivity psychosis was first described in a series of ten case reports of patients who had abrupt onset of psychosis upon the discontinuation of antipsychotic treatment[124]. The existence of this phenomenon has been controversial and only supported by small studies[125]. Nevertheless, there has been a recent resurgent interest in dopamine supersensitivity as a potential cause of the emergence of treatment resistance [123,124,126,127]. However, a meta-analysis of RCTs found no differences in relapse rates between abrupt and gradual antipsychotic withdrawal or between different antipsychotic doses prior to discontinuation[9]. Moreover, if dopamine hypersensitivity were a major reason for the lack of long-term efficacy, then the partial D2 agonist aripiprazole, which has not been associated with upregulation of dopamine D2 receptors, at least in adult animal models[128], should be associated with significantly lower relapse rates than full dopamine D2 antagonists, but there are no data to support this[129,130].

Comments

Overall, tardive dyskinesia is the clearest adverse clinical consequence in brain functioning of long-term antipsychotic treatment, which may be related to dopamine supersensitivity in a subgroup of vulnerable individuals. This risk should be evaluated when considering long-term antipsychotic treatment, and preventive strategies utilized. In addition, patients should be examined before initiating treatment to determine the presence of preexisting abnormal involuntary movements.

Other effects of long-term antipsychotic treatment on brain structure and function, particularly neuropathological changes and the risk of dopamine supersensitivity psychosis, are insufficiently substantiated. The current literature does not provide consistent evidence to support irreversible functional and structural brain changes as a consequence of long-term antipsychotic treatment other than tardive dyskinesia.

THE ROLE OF PSYCHOSOCIAL STRATEGIES IN MODIFYING THE RISK-BENEFIT RATIO OF ANTIPSYCHOTICS

While symptom reduction and response, as well as relapse prevention, are relevant outcomes, functional recovery is a preeminent goal of treatment in schizophrenia[39]. Unfortunately, when using criteria based on both clinical and social domains, recovery rates in schizophrenia have remained low, with a meta-analytically derived median of 13.5% across five decades, without improvement over time (although only two studies contributed data to the last decade)[131]. While, in an aforementioned meta-analysis[9], antipsychotic maintenance treatment was superior to placebo in preventing relapse with an NNT = 3, employment rates did not differ, pointing toward the need for psychosocial interventions to achieve improved functional outcomes.

A recent meta-analysis found a significant small to medium association between clinical outcomes and personal recovery, but psychotic symptoms – which are the main target of antipsychotic medications – showed a smaller correlation than affective symptoms with personal recovery[132]. These data underscore that antipsychotics alone are insufficient and that adjunctive multimodal psychosocial treatments are needed to help stabilized patients achieve personal recovery goals[133].

The Schizophrenia Patient Outcomes Research Team (PORT)[134] reviewed the evidence supporting a wide variety of psychosocial interventions for the long-term treatment of schizophrenia. The committee recommended eight psychosocial interventions with various indications and for different populations. Of these, cognitive behavioral therapy (CBT) was specifically recommended, with evidence supporting its efficacy in reducing positive, negative and overall symptoms in individuals treated with antipsychotic drugs[135]. While one of the goals of CBT is psychoeducation on antipsychotic drug adherence, the efficacy of CBT in improving this outcome has been inconclusive[136].

Interestingly, the evidence supporting the efficacy of CBT in reducing psychotic symptoms in individuals not taking antipsychotic medication[137], or individuals whose symptoms fail to respond to antipsychotic treatment[138,139], has been more consistent. This finding suggests that the impact of CBT goes beyond improving adherence with antipsychotic medications, having an antipsychotic effect on its own. However, to our knowledge, there have not been head-to-head comparisons of CBT with long-term antipsychotic dose reduction strategies that would provide data about CBT as a partial or total substitution for long-term antipsychotic treatment[139].

Family-based psychosocial treatments were another of the interventions recommended by the Schizophrenia PORT, with evidence for reducing relapses and rehospitalizations, and improving treatment adherence[134]. These interventions are based on psychoeducation, and are not generally conceived as partial or total alternatives to antipsychotics, but rather as augmentation. In a large Chinese study that randomized first-episode patients to antipsychotic treatment alone or augmented with family interventions for one year, those in the augmentation arm were less likely to discontinue antipsychotics, showed greater improvements in insight, social functioning and activities of daily living, as well as access to employment or education[140]. These results have been substantially replicated[141]. In a trial that compared family interventions augmenting regular or reduced antipsychotic dose, those treated with low-dose antipsychotics and family therapy were more likely to relapse than those with family therapy and regular antipsychotic dose[142].

More recently, the Recovery After an Initial Schizophrenia Episode - Early Treatment Program (RAISE-ETP) study tested the feasibility and effectiveness of the integration of various psychosocial and pharmacological interventions in the treatment of 404 first psychotic episode patients in 34 community clinics across the US[133]. This study compared coordinated specialty care (which included CBT-based psychotherapy, family education and support, supported education and/or employ-

ment, and guided pharmacotherapy) with treatment as usual, showing superiority of the former in improving quality of life, increasing time in education or at work, and reducing symptom severity[133]. Because pharmacotherapy also differed between the two compared conditions, it is difficult to draw firm conclusions regarding effects of specific modalities. However, it seems unlikely that the psychosocial interventions included in coordinated specialty care could serve as substitute to medications, rather than as an effective augmentation strategy, given the lack of differences in the antipsychotic dose used between the two arms[143].

While psychosocial interventions seem effective augmenting strategies, rather than partial or total alternatives to antipsychotics, they can help improve the long-term risk-benefit ratio of antipsychotics by improving symptomatic and psychosocial outcomes and by reducing the risk of cardiometabolic side effects. A meta-analysis of various non-pharmacological interventions, ranging from healthy lifestyle and behavioral interventions to CBT-based psychotherapies, demonstrated their effectiveness in significantly reducing body weight, body mass index and serum lipids associated with antipsychotic use[144]. Some of these advantages persisted over time. Unfortunately, challenges in engagement limit the effectiveness of these interventions[145,146].

Comments

Psychosocial interventions are effective augmentation strategies for the treatment of schizophrenia, particularly CBT-based interventions, which seem to have antipsychotic effects independent of improving antipsychotic adherence. These interventions can be effectively implemented beyond academic centers.

Evidence suggests that psychosocial interventions can improve the long-term risk-benefit ratio of antipsychotics by improving functional, recovery-focused outcomes and by decreasing the burden associated with antipsychotic treatment, rather than by necessarily allowing a decrease in antipsychotic doses.

INDIVIDUAL DIFFERENCES IN THE RISK-BENEFIT RATIO OF LONG-TERM ANTIPSYCHOTIC TREATMENT

While the diagnosis of schizophrenia has been associated with poor outcome and need for long-term antipsychotic treatment, the heterogeneity in response and illness course has resulted in calls to broaden the view towards a psychosis syndrome with variable outcome patterns[147,148]. Some studies suggest that a minority of patients could potentially discontinue antipsychotic treatment without risk of relapse. The literature indicates that this would apply to between 4% and 30% of the patients that are stabilized after an acute episode[43,48,52,149,150].

This variable range likely reflects heterogeneity in the studied populations, criteria for diagnosis and relapse, duration of follow-up, and exposure to non-pharmacologic interventions. Therefore, we need better epidemiological data and predictors of successful antipsychotic discontinuation in patients presenting with a psychotic syndrome consistent with a diagnosis of schizophrenia. Some studies have identified abrupt onset and older age, female gender, higher GAF scores, working, having a partner, living independently and the absence of substance abuse as significant predictors of better outcomes[43,149], whereas others have not been able to find any significant predictors[52].

A more consistent observation, however, is that previous successful antipsychotic withdrawal predicts successful withdrawal during follow-up[13,43,48,149]. This finding indicates that a minority of individuals with a psychotic syndrome fulfilling criteria for schizophrenia can successfully discontinue antipsychotic treatment, and the risk of relapse probably decreases as they move past a critical high-risk period for relapse. However, to date, there is no reliable evidence-based method to identify such individuals.

This question, however, may benefit from research that is being conducted aimed at patient-level prediction of treatment response. A wide range of predictors have been recently identified, involving genetic[151] and neuroimaging[152-154] perspectives. Also, individual risk scores based on clinical variables have been developed to predict transition from clinical high risk for psychosis to suprathreshold psychosis[155], and future research could develop similar models to predict treatment response. At present, despite some promising findings, the field is not ready to apply patient-level predictors of antipsychotic response in real-world care[156]. Future research should equally address the development of prediction models for successful treatment discontinuation.

Comments

To date there is no evidence-based strategy that enables us to identify individuals who would benefit from antipsychotic dose reduction or discontinuation with minimal increase in relapse risk. Future research should capitalize on the recent advances in patient-level predictors of treatment response in order to identify these low-risk individuals.

CONCLUSIONS AND RECOMMENDATIONS

Overall, antipsychotic maintenance treatment should be recommended for the mid term (i.e., 1-3 years), since there is strong evidence supporting efficacy of antipsychotics in reducing relapses over this time frame. Data on long-term outcomes are more equivocal and, although the effect of antipsychotics seems to decrease over time, this could be an artifact of long-term study designs. Increasing non-adherence and reverse causation may play a significant role in the observed time trends, while alternative hypotheses, including dopamine supersensitivity psychosis, are less well substantiated.

Additionally, mortality and neuropathological findings do not support an accrual of damage from cumulative antipsychotic dose and duration (with the exception of tardive dyskinesia). On the contrary, long-term antipsychotic main-

tenance treatment has consistently been associated with lower all-cause and specific-cause mortality compared to antipsychotic discontinuation in large national and representative samples of patients with schizophrenia.

Despite lack of long-term randomized, placebo-controlled trials and residual uncertainty regarding a subgroup of patients who fulfill criteria for schizophrenia and who may only suffer one single psychotic episode, it is reasonable to recommend antipsychotic treatment in the long term (i.e., >3 years), although with several additional suggestions. Continued antipsychotic treatment with ≥50% of the standard defined daily dose should be implemented (going below such doses increases the risk of relapse). LAIs should be prioritized to minimize breaks in treatment adherence, or to at least make them known, allowing for additional interventions to continue adequate treatment. Second-generation antipsychotics should be preferred over first-generation ones to minimize the risk of tardive dyskinesia. Psychosocial interventions, particularly CBT and family-based interventions, are useful as augmentation, even when there are residual or treatment resistant symptoms, yet these therapies are not a substitute for antipsychotic treatment. Some behavioral interventions can also be used to reduce some of the negative impacts of continued antipsychotic treatment (i.e., metabolic side effects).

In patients who have achieved successful antipsychotic discontinuation for <1 year, close monitoring is recommended, keeping in mind that only a minority of patients can successfully discontinue antipsychotics. There are no evidence-based methods to identify individuals who may be managed successfully with antipsychotic doses <50% of standard antipsychotic doses, or who can safely discontinue antipsychotics. Therefore, the recommendation to continue long-term treatment applies to patients in general. While it is recognized that shared decision making is relevant, clinicians should use the available evidence and discuss the risks of the illness and relapse-related biopsychosocial cost versus the risks of antipsychotic treatment, and clearly present the probability of relapse when stopping or continuing antipsychotic treatment. While the uncertainty is largest after the first episode of psychosis, following a second episode the arguments for antipsychotic maintenance treatment are even greater.

Future research should include predictive models of successful treatment discontinuation in addition to prediction of treatment response.

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