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The report of the joint WPA/CINP workgroup on the use and usefulness of antipsychotic medication in the treatment of schizophrenia

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Review

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Abstract

This is a report of a joint World Psychiatric Association/International College of Neuropsychopharmacology (WPA/CINP) workgroup concerning the risk/benefit ratio of antipsychotics in the treatment of schizophrenia. It utilized a selective but, within topic, comprehensive review of the literature, taking into consideration all the recently discussed arguments on the matter and avoiding taking sides when the results in the literature were equivocal. The workgroup's conclusions suggested that antipsychotics are efficacious both during the acute and the maintenance phase, and that the current data do not support the existence of a supersensitivity rebound psychosis. Long-term treated patients have better overall outcome and lower mortality than those not taking antipsychotics. Longer duration of untreated psychosis and relapses are modestly related to worse outcome. Loss of brain volume is evident already at first episode and concerns loss of neuropil volume rather than cell loss. Progression of volume loss probably happens in a subgroup of patients with worse prognosis. In humans, antipsychotic treatment neither causes nor worsens volume loss, while there are some data in favor for a protective effect. Schizophrenia manifests 2 to 3 times higher mortality vs the general population, and treatment with antipsychotics includes a number of dangers, including tardive dyskinesia and metabolic syndrome; however, antipsychotic treatment is related to lower mortality, including cardiovascular mortality. In conclusion, the literature strongly supports the use of antipsychotics both during the acute and the maintenance phase without suggesting that it is wise to discontinue antipsychotics after a certain period of time. Antipsychotic treatment improves long-term outcomes and lowers overall and specific-cause mortality.

Introduction

The modern medication treatment of schizophrenia appeared in the 1950s and had a profound impact on the lives of millions of patients and their families worldwide. The ability of these medications to both alleviate the acute episodes but also to prevent relapses made them a class of successful treatment options in the medical landscape.[1]

In the early 1960s, the antipsychotic treatment led Arvid Carlsson (1923-2018), who later received the Nobel Prize in 2000, to identify dopamine as a neurotransmitter, which in turn led to the dopamine hypothesis of schizophrenia.[2–5] In the 1990s, the second-generation antipsychotics (SGAs) or atypical antipsychotics appeared. Their main advantage was that they had a significantly lower frequency of extrapyramidal adverse effects and related conditions (eg, tardive dyskinesia or neuroleptic malignant syndrome).[6–10]

Thus, treatment with antipsychotics is currently considered to be the basis of the treatment of schizophrenia, and therapeutic approaches without the administration of these agents are definitely considered to be inappropriate.[11,12] Both for the acute and the maintenance phase, long-term antipsychotic treatment over years is accepted as the standard for patients with schizophrenia. While criticism on the methodology of research is always present and leads to improvement of the methodology itself,[13] recently it stopped being merely such a criticism. The

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core belief on the usefulness of antipsychotics has been challenged, and a series of publications argued that long-term antipsychotic treatment could not only be useless but also harmful, because it might worsen the long-term outcome of patients.[14–17]

In this frame, a number of issues have been raised, including the return of the dopamine sensitization hypothesis and tardive psychosis as well as the possibility antipsychotics to cause brain atrophy. These arguments emerged after the publication of several more recent studies, which revived an old debate and suggested a more favorable outcome for those patients who discontinued antipsychotic medication soon after the resolution of the acute phase.[18–20] Additionally, many authors insist on the possible harmful effects of long-term antipsychotic treatment.[16,21,22]

It is a fact that the literature lacks properly designed and conducted studies concerning the long-term effects of antipsychotics. Long-term studies of more than 2 to 3 years are naturalistic, and our knowledge beyond 3 years follow-up is limited.[23] However, the concern is so big that the possible harmful effect of antipsychotics on the brain has been included as a warning in the 2014 National Institute for Health and Care Excellence guidelines (CG178), albeit being mostly based on weak evidence.

Aim of the Paper

The aim of the current paper was to review the relevant literature and arrive at a consensus paper concerning the use and usefulness of antipsychotics as well as the limitations and potential dangers of their use in the treatment of schizophrenia. This document could serve as a guide for clinicians and also for patients and their families in the design of the long-term treatment approach as well as in the making of informed decisions.

Methods

The method followed for the writing of the current paper was

a. An analysis of arguments already published in the literature;
b. A selective review of the literature also in parallel with the analysis of these arguments. This literature review was not exhaustive; however, it was targeted at two main objectives:

- To establish a list of issues that have been raised during the last few years in the frame of the debate on antipsychotic use in people with schizophrenia and
- To find pro and con arguments to support or refute these issues.

The authors kept an open mind concerning what the actual conclusions from this endeavor could be and tried to cope with the literature in an as free of bias way as possible. The pro and con arguments had been processed according to the rules of evidence-based medicine.

Applying the methodology mentioned above, this report sought to address 10 clinically research questions detailed below.

Results

Question 1: Are antipsychotics efficacious and sufficiently safe during the acute psychotic phase?

There is a wide agreement on the efficacy of antipsychotics during the acute phase, and this is based on an abundance of hard data and among others a bulk of placebo-controlled studies, accompanied by a series of reliable meta-analyses.[24–28] However, the chance of achieving a treatment response to antipsychotics is greater in first-episode patients[8,29,30] than in multi-episode patients. The favorable efficacy of antipsychotics extends also into the early maintenance phase and up to 3 years after the acute episode with numbers-needed-to-treat vs placebo for relapse prevention being as low as 3.[23,31,32]

The data on antipsychotic efficacy are strong concerning total and positive symptoms, but equivocal concerning primary negative symptoms and neurocognitive deficits,[33–36] and this is particularly problematic since the progression of the disorder is characterized by the deterioration in these two particular domains of the clinical picture.

There are two main reservations against the acute use of antipsychotics: (1) that adverse effects of antipsychotics are too severe/that they are not safe and (2) that some patients might not necessarily need such treatment.[21]

It is clear that the acute treatment with antipsychotics can have a host of adverse effects, including neuromotor, endocrine, cardiovascular, and so on.[37–40] The same is true for longer term adverse effects, including diabetes, metabolic syndrome, and tardive dyskinesia.[9,10,41–43] It remains unclear, however, whether antipsychotics really increase the risk for cardiac arrhythmias and sudden cardiac death[44] or whether the increased mortality is due to increased medical morbidity[45–49] related to poor healthy lifestyle[46,50] and, possibly, underlying genetic/illness-related risk,[46] as well as underdiagnosis and undertreatment of cardiovascular risk factors[46] (complicating the propensity score adjustment vs control groups). Moreover, increased risk of serious somatic adverse events and of mortality associated with antipsychotics is mostly driven by elderly patients not diagnosed with schizophrenia[39,51,52] who may also be treated with other psychotropic medications.

Despite adverse effects of antipsychotics, it is clear that only subgroups of patients have adverse effects both acutely and long-term, while the "adverse effect" of an untreated schizophrenia illness pertains to all patients with this diagnosis, creating an overall positive risk–benefit ratio. This beneficial overall risk–benefit assessment is supported long-term by decreased overall mortality and, even, decreased cardiovascular mortality in nationwide samples of patients with schizophrenia treated with antipsychotics vs those not treated with antipsychotics.[53–57]

The second reservation, that is, that some patients may not need antipsychotic treatment, as they may stabilize even without antipsychotics, or not have any further psychotic episodes, is covered when addressing question 5.

Question 2: Should antipsychotics be used in first-episode patients?

There are a number of randomized controlled trials as well as meta-analyses[28,29,58] supporting the efficacy of antipsychotics in first-episode patients. In fact, the chance of achieving a treatment response to antipsychotics defined as at least minimal or defined as much/very much improvement is greater in first-episode patients, that is, 81% and 52% respectively[29] than in multi-episode patients, that is, 51% and 23% respectively.[8,30] However, there exists a subgroup of first-episode patients who have primary treatment resistance to currently available antipsychotics, with a frequency possibly of up to 25%.[59,60] Despite the overall positive treatment effects in first-episode patients, currently it is unclear what proportion of individual patients experiencing a first episode of non-affective psychosis will remit without medication, who they may be, and how long the remission will last.[61,62] Additionally, after taking into consideration the high relapse rate and related

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biopsychosocial consequences in first-episode patients,[12,63–66] the use of antipsychotic treatment in this group of patients seems necessary.

There is significant discussion recently concerning high-risk individuals and treatment options, especially antipsychotics, to prevent them from developing psychosis. The issue is far from resolved, partially because there are huge methodological problems; it seems most at–high risk individuals never progress to develop psychosis.[67] Those who do eventually develop psychosis seem to manifest neurocognitive deficits long before their first episode, and medication is not efficacious against these symptoms.[68,69]

The literature provides with some negative results concerning the efficacy of antipsychotic medication in the prevention of the first psychotic episode in high-risk persons[70-72] but also encouraging results do exist.[73-75] However, the quality of data is problematic and precludes definite conclusions.[71]

Question 3: Is there an antipsychotic discontinuation/withdrawal effect? What about the dopamine super-sensitivity hypothesis?

In the late 1950s and early 1960s, the hyperdopaminergic theory of schizophrenia was developed and it was based on the empirical discovery of antipsychotics and the theory that they produce their therapeutic effect by blocking post-synaptic D2 dopamine receptors.[76–78] Subsequently, a refined dopamine hypothesis was developed in the 1990s suggesting a subcortical hyperdopaminergic activity, being secondary to cortical hypodopaminergic activity, in particular in the frontal regions.[76,79]

It has been shown that there is no linear relationship between the D2 occupancy, clinical response, and side effects. Response appears with occupancy above 50% and extrapyramidal side effects when occupancy reaches 75% or more.[80–82] However, this idea has been challenged by the European First Episode Schizophrenia Trial (EUFEST) study which showed that with first-generation antipsychotics (FGAs) extrapyramidal adverse events might appear even at lower occupancy than the therapeutic threshold.[83]

Overall, the development of postsynaptic dopamine receptors supersensitivity has been documented in animals after repeated exposure to antipsychotics.[84-88] This led to concerns about possible long-term harmful effects in treated patients. A number of early naturalistic studies reported a favorable outcome and fewer relapses in patients with schizophrenia in direct negative correlation with the dosage of antipsychotics they were receiving. Furthermore, medication-free patients at endpoint seemed to have an even better outcome.[89-92] Although these were naturalistic studies and the outcome could well have been the result of the design rather than the intervention, with less severely ill or non-schizophrenia patients being off antipsychotics, the term "supersensitivity psychosis" was quickly coined to denote both the need for increasing dosages in order to maintain the therapeutic effect (tachyphylaxis) and the emergence of rebound psychosis after discontinuation of medication.[93–95] Supersensitivity psychosis predicts that relapse would be abrupt, and relapses will accumulate during the first couple of months after treatment discontinuation.

However, both after antipsychotic discontinuation[96] and on continued antipsychotic treatment,[97] gradual worsening of symptoms and slowly increasing relapse rated were observed, rather than an early peak of relapses, as would be expected with "dopamine supersensitivity psychosis."

The first meta-analysis to tackle this issue reported that there was no significant overall difference in the resulting survival functions for those patients who discontinued treatment abruptly vs gradually (N = 1006 and N = 204, respectively; $P > .10$).[98]

A more recent and more technically advanced meta-analysis also reported no difference between abrupt vs gradual discontinuation of either FGA or SGA medication.[99] A recent analysis of registry data from Finland did not support the supersensitivity psychosis theory either.[100] Moreover, two recent studies examining breakthrough psychosis during assured antipsychotic treatment with long-acting injectable antipsychotics were unable to find an association with either cumulative antipsychotic exposure[101] or increased antipsychotic doses.[102]

Overall, there seems to be some sensitization of dopamine receptors, at least in some patients who may also be sensitive to developing tardive dyskinesia and not respond as well to currently available antipsychotic medications, but this upregulation does not seem to cause a rebound psychotic exacerbation if antipsychotics are stopped either abruptly or gradually and does not seem to contribute to a worse global outcome in patients with schizophrenia, whose outcome is worst when not receiving antipsychotics.[53-55,100]

A special case of withdrawal is clozapine withdrawal syndrome, which is solidly proven concerning a variety of adverse events.[103] It has been reported that when discontinuation is abrupt, it could involve rebound psychosis,[104] delirium,[105] serotonin syndrome,[106] catatonia,[107-109] extrapyramidal adverse events, and neuroleptic malignant syndrome.[110–114] While the adverse events could be explained in terms of the pharmacodynamic profile of the substance, the rebound psychosis is far from proven since the hypothesis is based on a few case-reports only.

Question 4: Does initial treatment with antipsychotics worsen the long-term outcome?

The question whether initial treatment with antipsychotics might worsen the long-term outcome emerged soon after their discovery and their wide application in the treatment of psychosis[115] was recently supported by a narrative review.[116]

Nine relevant publications from the era when maintenance treatment was not utilized were identified in a recent paper[117] and come from three systematic reviews.[118-120] These papers followed first-episode psychotic patients long-term after their allocation during the acute episode to antipsychotics vs no pharmacotherapy. One of them was not published in a peer-reviewed journal. Their characteristics are shown in Table 1. These papers do not suggest a negative impact of initial treatment; on the contrary, they support a better outcome of patients on antipsychotic treatment.

As mentioned above, historical data from the era before the introduction of antipsychotics suggest that up to 30% of patients experiencing their first psychotic episode will recover spontaneously with remission being sustained in about 15% of them. The development of antipsychotics drastically improved the overall outcome by increasing remission rates twofold, but the effect on full recovery is less clear.[127–129] Statistics from Europe and North America show that antipsychotic treatment led to the dramatic decrease of asylum populations, but had a less impressive effect on the restoration of function. Similar results were produced by more recent studies from Ethiopia,[130] Indonesia,[131] and China.[132] All these studies reported that overtime the condition of untreated patients worsens more than in treated patients. A confounding variable could be that untreated patients today constitute the more severely ill and uncooperative subgroup of patients.[133] On the contrary, increased relapses, hospitalizations, and even mortality

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Table 1. Studies on the long term effect of initial treatment during the acute phase

Study	Design	Control	Follow-up	N Medication	N Controls	Mean Age	Males (%)	Results	Comments
[62]	MI	HI	Decades	287	213	NR	41.6	Treated did significantly better	Comparison of initially treated vs not after; double rates of complete remission in those treated (27.9% vs 14.6%, $P < .01$)
[121]	PR	Psychotherapy	3 y	92	89	NR	NR	NR ($P < .001$)[a]	Discharge was achieved in 58%-65% in psychotherapy and 95%-96% in medication arms
[122]	MI	HI	3 y	93	128	26-29 y	53.8	NS	Trend in favor of medication group
[123]	MI	HI	1-5 y	1979	2514	NR	NR	NS	Only first admissions; reports on any kind of psychosis (including organic); not specific for schizophrenia
[124]	MI	HI	4 y	170	NR	NR	NR[b]	Unknown	~10%-15% improvement of release rates; increase in readmission rates
[125]	MI	HI	5 y	50	50	31.7-32.6	39.0	Difference in response but not in remission rates ($P < .001$)	
[19]	PR	PLC	3 y	39	41	16-40[c]	100.0	Patients in the placebo arm and no medication afterward did better 3 y after the end of study ($P < .05$)	In terms of LOCF, the acute phase study would be negative; attrition rate was almost double in the placebo arm (45% vs 26%)
[90]	PR	PLC	1 y	270	74	28.2[d]	50.0[d]	Patients in the placebo arm did better 1 y after the end of study ($P < .05$)	Extreme difference in the dropout rate (2% in the medication arm vs 29% in the placebo group); those who received treatment after the trial did better at 1 y
[126]	Open randomized	Dose reduction	1 y	38	37	44.5	61.3	The dose reduction group did significantly better in most clinical outcomes	After correction for multiple comparisons, only negative symptoms seem to differ

Abbreviations: HI, historical data; LOCF, last observation carried forward; MI, mirror image; NR, not reported; NS, not significant; PLC, placebo; PR, prospective design.
[a]Calculated by the authors.
[b]42.9% males in the medication group.
[c]Range.
[d]Concern the original sample before removal of dropouts.

have been observed in untreated patients in meta-analyses and in generalizable nationwide samples.[53–55,66,100]

Taken all the above studies together, the data do not seem to suggest a deleterious effect of initial antipsychotic treatment; on the contrary there are at least some data suggesting a long-term beneficial effect and increased relapses, hospitalizations and even mortality in untreated patients. The studies reporting superiority of no treatment rely on placebo samples super-selected for benign outcome.

Question 5: Does maintenance treatment with antipsychotics worsen the long-term outcome?

The efficacy of maintenance treatment up to 1 year after the acute episode was confirmed by a meta-analysis of 65 trials.[23,99] Overall, it was reported that after 1-year follow-up, antipsychotic maintenance treatment was superior to placebo in terms of relapse rates (27% vs 64%) and rehospitalization (10% vs 26%). Furthermore, antipsychotic maintenance treatment was associated with lower likelihood of aggressive and violent behavior (2% vs 12%) and better quality of life. Total dropouts were fewer in the medication than placebo withdrawal arms (30% vs 54%). The beneficial effect of medication was unrelated to illness duration, previous discontinuations of medication, and duration of previous periods of stability, while FGAs and SGAs were equally efficacious. There was no difference between the active drug and the placebo in terms of employment, deaths, or dropout because of adverse events, although patients in the medication arm manifested significantly more extrapyramidal adverse events (16% vs 9%), sedation (13% vs 9%), and weight gain (10% vs 6%). The beneficial effect was similar in first-episode patients vs older/multi-episode patients.

The next milestone is treatment outcome at 3 years. The usefulness of maintenance treatment up until this period is again solidly established, although on the basis of far fewer data. The most recent study was a randomized trial in 128 first-episode patients who were stabilized on antipsychotics for 6 months. They were then randomized, to either a "drug discontinuation/drug reduction" group or a "standard drug maintenance" group. This was the first randomized study on the topic, but although the sample was drawn from an epidemiological cohort, only 50% of the first-episode psychosis (FEP) patients agreed to participate in the study. In only approximately 20% of patients, complete discontinuation was possible. The results suggested that discontinuing (or aggressively lowering) antipsychotic treatment during the maintenance phase led to a higher relapse rate (43% vs 21%) during the first 18 months.[134] These conclusions have been confirmed by later studies.[135,136]

The next question is whether further maintenance treatment could be beneficial or whether the risk of relapse tends to attenuate after a certain period of time. The data are insufficient but still suggest that the relapse rate was not different in patients who had been stable for up to 3 to 6 years. In other words, no matter how long the patient is doing well, the risk for relapse still exists and is uncovered after medication discontinuation. Thus, continuous treatment is necessary irrespective of current clinical status.[137,138]

The evidence for the effect of maintenance treatment with antipsychotics in patients with schizophrenia from observational and naturalistic studies is shown in Table 2.

Overall, small-scale observational studies suggest that patients currently off antipsychotics manifest a more favorable outcome.[18,141–144,148] The results from intermediate size studies are mixed.[145,153]

One particular study worth discussing is that of Wunderink et al[18] since it is the one considered to be strongly suggestive against the long-term use of antipsychotics that has stimulated the conduct of ongoing antipsychotic discontinuation and intermittent treatment studies that have produced significantly worse outcomes than maintenance studies.[154] After their initial 3-year follow-up study,[134] which concerned the randomization of patients to a dose-reduction (DR) or dose maintenance (MT) groups, the authors went on to naturalistically follow-up patients for an additional 5 years. At the end of that period, they reported (in 103 patients of the original 128) that there was no difference between the original group that was initially randomized to receive regular antipsychotic dose maintenance treatment and the group initially randomized to reducing the antipsychotic dose with an attempt to potentially discontinue the antipsychotic regarding relapse (68.6% vs 61.5%) or symptomatic remission (66.7% vs 69.2%). Additionally, there were no differences in number of relapses (1.13 ± 1.22 vs 1.35 ± 1.51), but the number of relapses was very low for the period of 7 years and thus it is suggestive of a very benign study sample, likely due to the fact that only 50% of the epidemiological sample had agreed to be randomized originally and, importantly, only 43.7% of the sample followed at 7 years had been diagnosed with schizophrenia 7 years ago. The reported greater likelihood of functional remission (46.2% vs 19.6%) and recovery (40.4% vs 17.6%; $P = .004$) in the antipsychotic DR/discontinuation group, but, again, the rate is unexpectedly high and suggestive of a very benign study sample. While there was a significantly lower antipsychotic dosage in the DR group (2.2 ± 2.27 vs 3.6 ± 4.01 mg haloperidol; $P = .03$), there was no difference in the months with zero intake of antipsychotics (6.38 ± 10.28 vs 4.35 ± 8.49; <7% of total time). The relapse rate was equal after year 3, being >60% and at the end of 7 years. This study manifests a number of problems. The major misleading feature of the study is that it discusses the results in terms of "medication discontinuation," while this is not the case. The original definition of the group was "dose reduction" (DR), and this indeed resulted in a significantly lower antipsychotic dosage in the DR group even at 7 years follow-up, but only 11 patients (11%) of the entire sample (DR: N = 8; MT: N = 3) were off antipsychotics for at least the last 2 years. The second problem is that only 43.7% of the patients had a diagnosis of schizophrenia, whereas the remainder had a non-schizophrenia and more benign form of psychosis, and that outcomes were assessed only via the phone and that diagnoses at endpoint were not confirmed. Another issue is that while they started as a randomized sample, this stopped at month 18 and from which point on the study sample followed a fully naturalistic course concerning treatment. Possible confounding factors could be that more patients with schizophrenia were randomly assigned to MT (51.0%) in comparison to DR group (36.5%), numerically more patients in the DR group were working at baseline (54% vs 36%; $P = 0.07$). Interestingly, the results do suggest a significant correlation between duration of untreated psychosis (DUP) and worse outcome (odds ratio [OR] = 0.62; $P = 0.02$).[18] These factors make it entirely unclear to what degree these data can be applied to the long-term outcome of patients with a confirmed schizophrenia diagnosis, and they do not sufficiently contribute to the question whether and in whom antipsychotics can be discontinued safely.

On the contrary, all large studies including epidemiological as well as nationwide registry-based data favor continuous maintenance treatment.[56,100,132,151,152] The harder the data, the more they favor continuous maintenance treatment, which strongly suggests the presence of significant confounding factors for the conclusions in observational and naturalistic studies, especially if no advanced

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Table 2. Studies on maintenance treatment beyond 3 years duration with antipsychotics in patients with schizophrenia

Study	Design	Control	Follow-up (up to)	N Medication	N Controls	Mean Age at Baseline[a]	Males (%)	Results	Comments
[139]	Retrospective	Not medicated after index episode with good outcome after 15 years	15 y	140	23	28.0	50.0	Approximately, 14.1% of patients with schizophrenia do well in the long term without any medication	Does not report on a comparison between medicated and unmedicated patients
[140]	Retrospective	—	25 y	644		NR	52.6	16.3% of patients with schizophrenia recover	The WHO International Study of Schizophrenia. Rejects the conclusions of the WHO IPSS
[141]	OBS	Not receiving medication at interview	15 y	40	24	23.0	67.0	Significantly higher recovery rate in patients not under medication (40% vs 5; $P < .001$)	The Chicago follow-up studies. Naturalistic design, it confirms that patients are prescribed and received medication only when necessary because of their clinical status
[142]	OBS	Not medicated after index episode	20 y	24	15	22.9	52.0	Those never medicated did significantly better	The Chicago follow-up studies. Naturalistic design, it confirms that patients are prescribed and received medication only when necessary because of their clinical status
[143]	OBS	Never on antipsychotic treatment	20 y	25	15	NR	NR	Significantly better course and outcome for the never treated group	The Chicago follow-up studies. Naturalistic design, it confirms that patients are prescribed and received medication only when necessary because of their clinical status. From the total sample, 21.4% did not need treatment
[144]	OBS	Never on antipsychotic treatment	20 y	25	15	NR	NR	Significantly better work functioning for unmedicated patients ($P = 0.001$)	The Chicago follow-up studies. Naturalistic design, it confirms that patients are prescribed and received medication only when necessary because of their clinical status
[145]	OBS	Treatment discontinuation	10 y	89	89	24.2	45.0	Significantly worse outcome in treatment discontinuation patients ($P = .012$)	75% with schizophrenia; at endpoint, a similar percentage of patients in the two groups were not taking antipsychotics. The groups were similar in all the other recorded variables at endpoint
[146]	OBS	—	20 y	175	—	28	59.5	Significant overall decline of functioning ($P < 0.001$); no effect of modifications in antipsychotic use ($P = 0.08$)	Suffolk County Mental Health Project Mixed sample of schizophrenia and schizoaffective disorders

Table 2. *Continued*

Study	Design	Control	Follow-up (up to)	N Medication	N Controls	Mean Age at Baseline[a]	Males (%)	Results	Comments
[147]	OBS	—	5 y	531	—	<30.0	50.9	Significantly better outcome in developing countries	The WHO IPSS
[148]	OBS	Not medicated in previous 3 months	10 y	46	24	34	54.3	Significantly better course and outcome for the non-treated group during the last 3 mo	patients with schizophrenia were more likely to refuse participation; 83% of the study group suffered from Schizophrenia; almost all were receiving medication within the previous year; confirms that patients are prescribed and received medication only when necessary because of their clinical status
[148]	OBS	Not receiving medication at interview	8.7 y	46	24	34.0	54.3	Significantly more non-medicated patients were in remission (60% vs 20%; $P < .001$)	83% were suffering from schizophrenia
[149]	OBS	—	10 y	532	—	30.8	57.9	22.6% of initial sample recovered, 7.8% died	The AESOP-10 study, 75% schizophrenia
[132]	OBS, epidemiological data	Not medicated after index episode	14 y	371	118	40.0	40.0	Significant higher remission rates in medicated patients (34.1% vs 16.4%) and lower mortality rate (29.6% vs 43.2%) both at $P < .01$	Based on epidemiological data of 123,572 persons from China, 1994
[150]	OBS	—	10 y	532	—	30.8	57.9	8% of initial sample had no episodes, 26.3% recovered, and 7% died	The AESOP-10 study, 75% schizophrenia
[151]	OBS, registry data	Not medicated after index episode	3.6 y	1433	797	30.7	62.0	Significantly better outcome and lower mortality in the medication group	Nationwide cohort of 2230 consecutive adults hospitalized in Finland for the first time
[152]	OBS, registry data	Never medicated	11 y	47 967	18 914	51.0	46.0	Lower mortality for current as well as long-term medication use ($P < .001$)	Nationwide registry data cohort of 66 881adults hospitalized in Finland between 1996 and 2006
[100]	OBS, registry data	Treatment discontinuation	20 y	4217	3217	35.0	56.5	Significantly more frequent worse outcome in the discontinuation group (56.5% vs 34.3%) and higher mortality rate (HR > 2.7)	Nationwide registry data cohort of adults hospitalized in Finland between 1972 and 2014
[56]	OBS, registry data	Not medicated after index episode	5 y	21 492 and 1230 FEP	2077 and 232 FEP	45.5 and 36.3 in FEP	61.0 and 66.0 in FEP	Significantly higher overall mortality and specifically due to	Nationwide registry data cohort of 7,040,632 people living in Sweden in 2005

Table 2. *Continued*

Study	Design	Control	Follow-up (up to)	N Medication	N Controls	Mean Age at Baseline[a]	Males (%)	Results	Comments
								cardiovascular events in patients with no antipsychotic exposure and high exposure vs the rest. The highest excess overall mortality was among FEP patients with no antipsychotic use	
[153]	OBS	Not receiving medication at interview	10 y	182	121	26.3	55.4	Significantly higher remission rate in completers not under medication (74.4% vs 48.5%)	Danish OPUS-cohort, 80% with schizophrenia, almost half lost to follow-up. Extreme rates of remission
[18]	Open, naturalistic	Dose reduction group	7 y	51	52	26.0	NR	Significantly higher recovery rates in the dose reduction vs the medication group (40.4% vs 17.6%; $P = 0.004$)	Less than 45% of the study sample were suffering from schizophrenia

Abbreviations: FEP, first-episode psychosis; IPSS, International Pilot Study of Schizophrenia; WHO, World Health Organization.
[a]For several studies, it is only indicative or approximate calculations by the authors.

propensity score matching or within subjects designs are employed to mitigate against relevant selection biases.

In the literature, there are several impressive studies with strange results. One such example is the World Health Organization International Study of Schizophrenia, which among other things reported that schizophrenia had a more favorable outcome in developing countries.[140,147,155] This would indirectly imply that treatment-naïve patients might do better long-term, but subsequent publications rejected this more favorable outcome.[156–159] Maybe, the most important finding of that study was that the time spent in episodes of psychosis during the early illness stages is a strong determinant of later adverse outcomes, thus supporting the long-term beneficial effect of early and sufficient medication treatment.[140]

A number of projects, including the AESOP-10,[149,150] the Suffolk County Mental Health Project,[146] and the Chicago Follow-up studies,[141–144] failed to provide data and conclusions free of the well-known biases of naturalistic and observational studies. One recent, large registry study with up to 20-year follow-up (median = 14 years) showed a significantly lower mortality rate for patients during any vs no antipsychotic treatment (25.7% vs 46.2%).[54]

The conclusions from the review of the above studies by several authors are conflicting.[12,16,117,160] Taken together, the above simply confirm the known properties of observational and naturalistic design, which is characterized by a number of inherent biases and a number of confounding factors since no adequate control group is included,[161] while the direction of the cause-and-effect relationship is impossible to determine. A minority of patients probably around 10% to 15% could do well with very low dosages and possibly intermittent administration of antipsychotic treatment with prolonged periods without any antipsychotic medication; however, it is yet impossible to identify a priori these patients.[12] The argument that a relevant minority of patients with a confirmed diagnosis of schizophrenia will do well long-term without any medication ever[162,163] is not supported by the data.

Inconsistencies in the data and interpretation most likely depend a lot on the selection of patients with different psychotic disorders, which must be taken into consideration when attempting to make judgments about risk and benefits of antipsychotic treatment in patients with schizophrenia.

Finally, as mentioned above, long-term adverse effects of antipsychotics clearly exist,[9,10,32,41–43] including diabetes, metabolic syndrome, and tardive dyskinesia. Moreover, patients with schizophrenia have a 1.5 to >2-fold increased risk of mortality compared to the general population.[45,46] However, the mortality risk is significantly higher/elevated in patients not receiving antipsychotic treatment compared to those undergoing long-term antipsychotic treatment.[53–57] Importantly, both for hospitalization risk and all-cause mortality, there does not appear to be a safe time when to discontinue antipsychotic treatment after a first episode of schizophrenia.[100]

This, in conclusion, the currently available data support the positive risk–benefit ratio of long-term antipsychotic treatment in people with schizophrenia.

Question 6: Does the relapse rate level off after 3 years irrespective of treatment?

This suggestion is based mainly on the results of the second naturalistic phase of the Wunderink et al study.[18] As discussed previously, that study sample was unusually benign in terms of diagnosis and illness course, with no more than half of its study sample suffering from schizophrenia, and it is an antipsychotic dose reduction rather than a discontinuation study with the two

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arms being similar in terms of treatment after a certain period of time and at endpoint. This is expected because of the naturalistic design since after some time, the maintenance treatment was adjusted to the individual needs of each patient, independent of initial randomization up to 7 years prior to endpoint, resulting in the flattening of differences between the two relatively benign outcome groups.

A number of other studies, including a meta-analysis[164] and primary data studies,[146,149,165] also utilized mixed samples and therefore unfortunately add little to the effort to answer the question on the longitudinal course of relapse rates in people with diagnosed schizophrenia (as opposed to a mix of psychotic conditions). The overall picture that these studies provide is that "schizophrenia" (although defined in an overinclusive way) is characterized by a chronic and deteriorating course. It is important to note that a chronic illness course and poor functionality may occur despite less frequent exacerbations and episodicity of the illness.

In summary, the authors are not aware of high-quality data to support the claim that the relapse rates level off after 3 years, but clearly more research is needed on this topic.

Question 7: Is long DUP a negative predictor for the outcome?

Although it is common belief that a long DUP could constitute a negative predictor, this belief has been challenged recently especially in the frame of care of psychotic patients without the use of medication.

In general, mostly older meta-analyses[166–168] and individual studies converge on a consensus that longer DUP is modestly related to positive and negative symptoms as well as several indices reflecting worse functioning and poor remission both at baseline and after treatment and follow-up but not with neurocognitive function (Table 3). Only 2 out of the 14 studies of Table 3 suggest no negative effect for DUP.[18,169–181] It is interesting that even the second phase study by Wunderink et al, which is the only study that utilized a randomized study sample at baseline, reported that shorter DUP was in essence the only variable that was significantly related to symptomatic remission (OR = 0.62; $P = .02$).[18]

Criticism concerning three specific papers[167,168,177] argues that treatment is not synonymous with antipsychotic treatment, and therefore the only point that the literature suggests is that if patients are identified early, they tend to be less impaired and they remain so over time, but this does not necessarily mean that an earlier intervention of any kind has much effect.[162] However, this shifts the attention from the importance of DUP to the efficacy of acute and long-term treatment, which are quite different issues. Criticism for the conclusions of the Norwegian Early Detection (TIPS) study[175,177] argues that results are mediated by the patients' premorbid status.[21] An additional concern was expressed on the unexpectedly high death rate in this young patient sample,[182] but this was related to longer DUP and substance abuse, although there was also an unusually high 1% death rate because of cardiovascular problems.[183]

There are a number of meta-analyses on the topic. The first of them identified 43 publications and reported that shorter DUP was associated with negative symptoms alone at treatment initiation and with greater response to treatment, global psychopathology, positive and negative symptoms, and functional outcomes. There was no correlation with neurocognitive deficits, and the findings remained significant after controlling for variables known to influence prognosis.[168]

The second included 26 studies involving 4490 patients; it showed a significant association between longer DUP and several poorer outcomes at 6 and 12 months (including total symptoms, depression/anxiety, negative symptoms, overall functioning, positive symptoms, and social functioning). Additionally, patients with a long DUP were significantly less likely to achieve remission and controlling for premorbid adjustment did not influence the findings.[166]

Another meta-analysis of 33 studies reported that long DUP was associated with more severe outcome in general symptomatology, positive and negative symptoms, social functioning, and remission but not in hospitalization, quality of life, or employment. Longer follow-up resulted in stronger associations between DUP and negative symptoms ($P = .035$), hospital treatment ($P = .046$), and global outcome ($P = .035$). Higher national income level resulted in a stronger correlation between DUP and general symptomatic outcome ($P = .008$) and positive symptoms ($P = .016$).[167]

A more recent meta-analysis of 27 studies and 3127 patients with FEP that focused exclusively on neurocognition reported that, overall, DUP and neurocognitive abilities were not significantly related, with the exception of evidence for a weak relationship with planning/problem-solving ability which will probably not survive correction for multiple comparisons.[184] The last meta-analysis focused on the possible relationship of DUP and brain structure. It identified 48 studies and reported that only a small minority of them reported a statistically significant finding.[185]

It is interesting to mention a recent study which suggests that the frequently reported association between DUP and psychosocial function may be an artifact of early detection, creating the illusion that early intervention is associated with improved outcomes. In other words, according to these authors, DUP may be better understood as an indicator of illness stage than a predictor of course.[186]

In conclusion, the literature suggests that longer DUP is modestly related to positive and negative symptoms as well as several indices reflecting poor functioning and reduced proportion of remission both at baseline and after treatment and follow-up, but the effect on neurocognitive functioning is equivocal. The data on the possible neurotoxic effect are less robust, and they seem to depend on the imaging methodology and probably concern specific brain regions rather than the whole brain, but more data are needed. One reason why the literature fails to define the role of DUP is that the progression of schizophrenia is slow and it takes many years for worsening to appear.[187]

Question 8: Are relapses detrimental to illness trajectories and outcomes?

Overall, the classical concept of schizophrenia is that of a chronic illness with frequent relapses leading to significant disability.[188] Relapses are considered to exert a neurotoxic effect with patients never returning to their previous functioning status.[120,189–191]

There is no reliable way to predict which patients will relapse with the use of either clinical or neurobiological indices[192] and, as mentioned above, longer duration of treatment does not reduce the risk of relapse upon antipsychotic discontinuation.[192]

The suggestion that the accumulation of relapses leads to disease progression is supported by the following findings:

- First episodes respond better to treatment and have better prognosis in comparison to later episodes.[189]
- First episodes require lower dosages of antipsychotics.[193]
- Time to remission increases for each subsequent episode.[190]
- With accumulation of relapses, a rather abrupt way of relapsing seems to emerge, which probably is suggestive of the development of a reduced threshold for psychotic decompensation.[194]

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Table 3. Studies on the effect of DUP on the long term outcome in patients with schizophrenia

Study	Follow-up (up to)	N Medication	Mean DUP	Mean Age at Baseline[a]	Males (%)	Results	Comments
[169]	1 y	200	84.2 wk	24.8	68.0	Significant effect of DUP on the outcome concerning positive symptoms and quality of life ($P < .001$)	Calgary Early Psychosis Program, quasi-epidemiological sample
[170]	5 y	296	142 wk	25.1	50.3	No significant effect of DUP on the outcome	OPUS, 94.6% schizophrenia
[171]	1 y	85 FEP	52.5 wk	NR	NR	Significant effect of DUP on the outcome concerning positive and negative symptoms ($P < .003$) but not neurocognitive	West London First Episode Schizophrenia Study
[172]	9.7 wk	196	~32–40 wk	34.3	51.5	DUP >12 months was significantly related to poor outcome ($P < .005$)	77.5% schizophrenia
[173]	8 wk	71 FEP patients and 73 healthy controls	25.4 wk	25.2	54.9	Significant association of DUP and left hippocampal atrophy both at baseline and accelerated after 8 wk	
[174]	1 y	57 (27 short and 30 long DUP) and 30 controls	35 wk	25.5	55.2	Long DUP patients differed from controls in the volume of gray matter in bilateral parahippocampus gyri, right superior temporal gyrus, left fusiform gyrus, left middle temporal gyrus, and right superior frontal gyrus ($P < .05$) and from short-DUP in right superior temporal gyrus, left fusiform gyrus, and left middle temporal gyrus ($P < .01$)	Findings probably would not survive correction for multiple comparisons
[175]	10 y	281 FEP	12.6 wk	28.5	59.0	Significantly more patients in the early detection group recovered (30.7% vs 15.1%, $P = 0.017$)	The Norwegian Early Detection (TIPS) study, less than 65% suffering from schizophrenia. Less patients in the early detection group dropped out. Findings do not survive correction for multiple comparisons
[176]	—	156 FEP	74.3 wk	25.8	62.2	No significant effect of DUP on neurocognitive function and brain MRI	Iowa Longitudinal Study, 73% schizophrenia
[177]	2 y	231 FEP	10.4 wk	28.5	NR	The early detection group was significantly better in the negative, depressive, and neurocognitive symptoms ($P < .001$)	The TIPS study; *N* of schizophrenia cases unknown, probably 65%
[178]	25 y	80	196 wk	47.9	65.0	Patients with DUP less than 1 y had more favorable outcome (28.9% vs 8.6%; $P = .025$), less hospitalizations (85.7% vs 62.1%; $P = 0.049$) and a better functioning (GAF: 50.32 ± 16.49 vs 40.26 ± 9.60, $P = .002$)	All cases with schizophrenia; only difference in functioning would survive correction for multiple comparisons
[179]	1 y	43	24 wk	36.7	34.9	Long DUP correlated with higher need for hospitalization at the time of first diagnosis (52% vs 9%; $P = 0.002$), re-hospitalization (67% vs 32%; $P = .022$) and worse functioning after 4 y (SDSS: 7.0 ± 5.2 vs 3.4 ± 4.9; $P = 0.035$)	All cases with schizophrenia; only difference in hospitalization at first diagnosis would survive correction for multiple comparisons
[180]	14 y	209	<26 wk	41.0	43.0	Shorter DUP (≤6 months) related to significantly lower suicide attempts, shorter illness duration, and higher full remission rate. No differences were found regarding survival and homelessness. Longer DUP (>6 months) was significantly associated with higher negative and general mental scores (all at $P < .05$)	Based on epidemiological data of 123,572 persons from China, 1994. Probably nothing survives after correction for multiple comparisons
[181]	1 y	2134	<26 wk	23.3	67.4	DUP was related to positive symptoms ($P < .001$), worse recovery ($P < .001$), and worse global functioning ($P = 0.035$). There was some evidence for an inverse correlation with negative symptoms also	From the National EDEN which is a UK-based cohort; only 41.2% schizophrenia
[18]	7 y	103	38 wk	26.0	NR	Only shorter DUP was related to remission ($P = 0.02$)	Less than 45% of the study sample were suffering from schizophrenia

Abbreviations: FEP, first-episode psychosis; DUP, duration of untreated psychosis; MRI, magnetic resonance imaging; NR, not reported.
[a]For several studies, it is only indicative or approximate calculations by the authors.

- Refractoriness accumulates at a rate of 16% for each subsequent episode,[195] with recent studies confirming loss of antipsychotic response after a relapse in a subgroup of patients.[65,196]
- The development of an abrupt way of relapse in combination with the accumulation of refractoriness over time[59,197] is consistent with the development of sensitization and a "kindling" model.
- Long-term disability correlates with the number of relapses.[198]
- Reduced gray matter volume is related to total episode duration, but not to the number of relapses.[199]
- The observation that the rate of deterioration is higher at the early phase of the disorder is in accord with a recent model, which suggests that mainly the early phase of schizophrenia is characterized by psychotic symptoms.[187]

Conversely, the following arguments are against such a suggestion:

- Deterioration has begun already before the onset of florid psychotic symptoms, during the premorbid period.[200,201]
- The deterioration accumulates rapidly during the early years, but tends to reach a plateau later in the illness course,[202] although there are no convincing data to support a leveling-off of the relapse rate. As discussed above, this could be the result of the predominance of psychotic symptoms early in the course of the disease while after several years they tend to attenuate.[187] Another explanation could be that the accumulation of the deficit is not linear and will level off at some point.
- The difference in response rates between first and later episode patients with schizophrenia is likely small.[203–206] One meta-analysis in first-episode psychotic patients reported an overall response rate (50% reduction in scale score) of 81.3% (95% confidence interval [CI] = 77%-85%),[207] while another one in chronic schizophrenia patients with a solid diagnosis of schizophrenia reported a similarly defined response rate being at 51% (95% CI = 45%-57%).[8] The biggest problem for the interpretation of these results is that the majority of patients of the FEP samples do not seem to suffer from schizophrenia defined according to Diagnostic and Statistical Manual of Mental Disorders criteria (ie, 6 months requirement of the overall illness), making a valid direct comparison impossible.

Overall, the literature supports the concept that relapses correlate with worse long-term outcome. Continuous antipsychotic treatment is necessary in order to avoid relapses since their way of appearance usually precludes early intervention and immediate resolution of symptoms.[12] Probably, relapses are not the only reason of disease progression and their effect is not linear, but instead it is stronger during the first few years after the disease onset. Unfortunately, this is the period when both patients and their therapists are usually inclined to stop long-term maintenance treatment.

Question 9: Is there a brain volume loss in patients with schizophrenia and what are its causes?

Cross-sectional findings

The first reports with the use of brain CT on possible brain structural change in patients with schizophrenia[208] faced negativistic criticism and rejection on the basis of circular logic and theoretical–ideological arguments.[209] The psychiatric community of the time found it difficult to accept that patients manifested observable brain damage.

Some imaging studies report strong significant differences between patients and controls,[210–213] while others do report significant differences but those would not survive correction for multiple comparisons.[174,214–216] There are also some data in at-risk subjects indicating that brain imaging could be of prognostic usefulness for the identification of those persons at high risk that will eventually develop psychosis.[217,218] A meta-analysis on cross-sectional volumetric brain alterations in both medicated and antipsychotic-naive patients included 317 studies comprising over 9000 patients. In the 33 studies, which included antipsychotic-naive patients (N = 771), volume reductions in caudate nucleus and thalamus were more pronounced than in medicated patients. White matter volume was decreased to a similar extent in both groups, while gray matter loss was less extensive in antipsychotic-naive patients. Gray matter reduction was associated with longer duration of illness. According to these findings, brain loss in schizophrenia is related to a combination of (early) neurodevelopmental processes—reflected in intracranial volume reduction—as well as illness progression. Most of the observed significant results would survive correction for multiple comparisons.[219]

Overall, the imaging data are strong in suggesting that schizophrenia is characterized by loss of total gray matter volume which is probably more pronounced in the temporal lobes. Data concerning other brain regions and structures are relatively weak. It seems that a reduction in interneuronal neuropil in the prefrontal cortex is a prominent feature of the cortical pathology in schizophrenia which is characterized by subtle changes in cellular architecture and brain circuitry that nonetheless have a devastating impact on cortical function. Most volume changes that occur appear to be the result of reduction in neuropil related to less dendritic branching, lower spine density, and smaller cell body size.[220] Representative studies are shown in detail in Table 4.

These brain abnormalities seem to be present already at illness onset. This was the conclusion of the Edinburgh High Risk Study (though of doubtful strength because of the presence of multiple comparisons).[231] However, these data were solidly supported by a more recent study, which found that the left hippocampal volumetric integrity was lower in the FEP group ($P = .001$) at baseline.[173] This conclusion is supported by a meta-analysis of 43 studies and MRI data from 965 FEP patients matched with 1040 controls which reported the presence of gray matter volume loss in the temporal lobe of patients with schizophrenia already at disease onset.[232]

The data from postmortem neuropathological studies are equivocal. Some studies definitely report no significant difference between patients with schizophrenia and controls,[221,226,230] others definitely report significant reduction in the number and density of neurons and maybe of glia in the neocortex,[224,225,227-229] while some other studies reported significant differences, but these were of questionable strength.[222,223] Overall, these data suggest that there is no strong histopathological evidence to support the presence of a neurodegenerative or neurotoxic process, including neuronal loss, ubiquitination, dystrophic neurites, astrocytosis, or microglial infiltrates.

Longitudinal findings

Most studies on the longitudinal course of schizophrenia suggest the progressive loss of brain volume.[173, 211, 212, 215, 231, 233–235] Some authors do not report such a finding,[236] while others lose their power after correction for multiple comparisons.[199,213,214] The most frequent and reliable findings concerned total brain volume, ventricular enlargement, frontal and temporal gray matter, and the nucleus caudatus. Some data also implicate the thalamus and the hippocampus. The studies in first-episode patients argue that the findings exist

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Table 4. Studies on Structural Brain Changes in Patients with Schizophrenia vs Controls

Study	Patients with Schizophrenia	Controls	Results	Comments
Postmortem studies				
[221]	23	14	No difference	
[222]	13	9	Significantly smaller hippocampus, parahippocampal gyrus, amygdala, and internal pallidum bilaterally in patients	No significance after correction for multiple comparisons
[223]	18	21	Significantly smaller hippocampus and internal pallidum bilaterally in patients	No significance after correction for multiple comparisons
[224]	15	15	In patients, no changes in clustering of neurons or glia. Neuronal somal size was reduced in layer 5 (18%, $P = 0.001$), neuronal density was increased in layer 6 (61%, $P = 0.006$) and in layer 5 (33%, $P = 0.003$)	From the Stanley Foundation Brain Consortium
[225]	7	7	A 28% decrease in total numbers (or densities) of cortical layer III oligodendrocytes and a 27% decrease in the white matter of Brodmann's area 9 in the superior frontal gyrus	Some of these findings survive correction for multiple comparisons, depending on the method (CNPase immunostaining, Nissl and CNPase immunohistochemistry)
[226]	8	16	No difference in neuron numbers in the neocortex	
[227]	16	19	In area 9, neuronal density was increased in layers III to VI; cell packing of pyramidal and nonpyramidal neurons was elevated ($P < .002$ and $P < .01$). The largest increases (24%) were observed in layers IV and V.	The findings for pyramidal but probably not those for nonpyramidal neurons will survive correction for multiple comparisons
[228]	14	19	Significantly smaller frontal gray matter volume in pts vs controls (12%; $p = 0.01$). No other difference existed	The finding survives correction for multiple comparisons.
[229]	12	14	Significantly smaller number of glial cells in in Brodmann's area 24 (33%, $P = 0.007$). No other finding was significant	The finding survives correction for multiple comparisons
[230]	8	10	No difference in neuron numbers and density in the PFC	
Neuroimaging studies				
[210]	15 MZ and 14 DZ twins discordant for Schizophrenia	29 healthy twins	Significantly smaller whole brain volume for patients ($P < .001$) and co-twins ($P < .05$) in comparison to controls. Patients also differed from co-twins ($P < 0.05$). Lateral ventricles were larger in patients than in their co-twins (14.4%; $P < .01$)	Significant differences also between healthy twins and controls, suggesting the existence of an endophenotype
[214]	16	20	Two brain MRI with a 1-y interval. At baseline, patients differed from controls in terms of putamen and third ventricle size ($P < .01$). After 1 y, the acceleration of volume loss was evident between patients and controls concerning total gray ($P = .04$) and white matter ($P = .02$) and nucleus accumbens ($P = .05$) and caudatus ($P = .03$). Patients who discontinued medication manifested greater volume loss in the nucleus accumbens ($P = 0.04$) and the putamen ($P = 0.01$)	No difference would survive correction for multiple comparisons
[174]	57 (27 short and 30 long DUP)	30	Significant difference in the volume of gray matter in bilateral parahippocampus gyri, right superior temporal gyrus, left fusiform gyrus, left middle temporal gyrus, and right superior frontal gyrus ($P < .01$)	No difference would survive correction for multiple comparisons
[213]	84	116	After 3 years follow-up, in patients there was a significantly greater change in the cerebral gray matter volume ($P = .006$) and cortical volume ($P = .03$) and thickness ($P = .02$), in cortical volume and thickness of the right supramarginal, posterior superior temporal, left supramarginal, left postcentral, and occipital regions (P values between <.001 and .03 after clusterwise correction). Findings were independent of medication and substance abuse	

Table 4. *Continued*

Study	Patients with Schizophrenia	Controls	Results	Comments
[215]	107	20	MRI scans at baseline and after 18 months. At both time points, patients had larger total ventricular volumes ($P = .019$), larger lateral ventricular volumes ($P = .036$), larger third ventricles ($P = .036$), and smaller anterior hippocampal volumes ($P = .01$)	No difference would survive correction for multiple comparisons
[216]	56	90 healthy relatives and 55 controls	Patients displayed enlargement of the third ventricle ($P < .01$)	No difference would survive correction for multiple comparisons
[212]	93	113	5-years follow-up. Significantly thinner cortex in the left orbitofrontal and right superior temporal cortex and parahippocampal gyrus in patients compared with controls ($P < .001$). At follow-up, in patients, the decrease in mean cortical thickness across the brain was significantly more pronounced ($P < .001$)	All findings corrected for multiple comparisons
[211]	33	71	9-y follow-up. Significantly more volume loss in patients ($P = 0.003$) especially in the temporal lobe and periventricular area	Northern Finland Birth Cohort 1966

Abbreviations: AD, Alzheimer's disease; DZ, dizygotic; MRI, magnetic resonance imaging; MZ, monozygotic; PFC, prefrontal cortex; PM, postmortem.

before the initiation of antipsychotic treatment and progress semi-independently of treatment. Representative studies are shown in detail in Table 5.

A meta-analysis identified 19 studies, analyzing 813 patients with schizophrenia and 718 healthy controls and reported that over time, patients with schizophrenia showed a significantly higher volume loss of total cortical gray matter, left superior temporal gyrus (STG), left anterior STG, left Heschl gyrus, left planum temporale, and posterior STG bilaterally. Meta-analysis of FEP patients showed a more significant pattern of progressive loss of whole cerebral gray matter volume involving the frontal, temporal, and parietal lobes and left Heschl gyrus compared with healthy controls. Progressive cortical gray matter changes in schizophrenia occur with regional and temporal specificity, and the underlying pathological process appears to be especially active in the first stages of the disease, and affects the left hemisphere and the superior temporal structures more.[237]

Data suggest associations between reduced total and regional brain volume and poorer outcomes,[238] including greater negative symptoms and cognitive performance.[239]

Question 10: Does antipsychotic treatment cause brain volume loss?

As soon as the first reports on ventricular enlargement in patients with schizophrenia were published,[208] one of the first comments was that this was a consequence of antipsychotic medication treatment.[91] Since then several authors have attributed these findings to treatment with antipsychotics, cannabis use, diabetes, and hypertension.[239–242]

Animal studies definitely suggest that exposure to antipsychotics leads to 6% to 15% brain volume reduction.[243–245] The biggest problem in the interpretation of these results is that experimental animals do not suffer from schizophrenia; at best, they correspond to a model that tries to mimic some aspects of schizophrenia but otherwise they are "healthy."[246] Furthermore, the effect of antipsychotics on the brain of non-schizophrenic animals is too strong and beyond doubt, while on the contrary the progressive brain volume reduction after FEP is very small.[241] The effect size for the only index which was found in human studies to be significant, that is, whole brain gray matter, ranges approximately from 0.14 (not significant after correction)[240] to 0.36,[219] while in animal studies the findings are strongly significant and for the total number of cells the effect size was 0.89[244] or >10% loss.[246,247] If brain volume reduction was due to antipsychotic medication, it should have been much more pronounced, global, and much more clearly correlated with medication, which is not the case. Moreover, there is only regionally circumscribed cell loss in humans supported by stereological cell number estimations. These findings support a loss of oligodendrocytes in the prefrontal cortex (area BA9)[225] and CA4 subregion of the hippocampus.[248,249] Additionally, a recent meta-analysis showed increased microglia density with focus in the temporal cortex.[250] Hence, because this cell loss is minimal and localized, the change in brain volume is attributed mainly to neuropil volume loss.[251] There is no similarity between the findings from the brains of patients with schizophrenia and animal studies neither in terms of quantity nor in terms of quality in contrast to what some authors insist on.[163]

There is no "creationist creed" in this interpretation; it is the difference between normal and abnormal physiology. In the wider field of medicine, there are several treatments that protect the patient from the harmful effects of the disease process, but if they are given to healthy individuals (or individuals without the specific

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Table 5A. Studies on the Long-Term Progression of Structural Brain Changes in Patients with Schizophrenia vs Controls

Study	Patients with Schizophrenia	Controls	Follow-up	Results	Comments
[236]	33	31	6-9 mo	No difference at baseline or follow-up	
[199]	202		7 y	Significant decrease in total brain volume ($P = .01$), and in frontal ($P = .04$) and temporal ($P = .03$) gray matter	Iowa Longitudinal Study. Results do not survive correction for multiple comparisons
[214]	16	20	1 y	Patients manifested a significant decrease in total gray ($P = .04$) and white matter ($P = .02$), and the nucleus caudatus ($P = .03$) and accumbens ($P = .05$)	Results do not survive correction for multiple comparisons
[173]	31	32	8 wk	Left HVI significantly decreased in patients in comparison to controls ($P = .001$). The change in left HVI was inversely associated with DUP ($r = -0.61$; $P = .002$)	The study utilized a unique imaging method
[235]	119	—	3 y	Met-allele-carriers showed a significant decrease in frontal gray matter volume ($P = .04$), lateral ventricles ($P < .0003$)	Iowa Longitudinal Study. Only the finding concerning lateral ventricles survives correction for multiple comparisons
[234]	211	—	7 y	Significant decrease in total, frontal, and parietal gray matter ($P < .001$) as well as temporal ($P < .01$), parietal white matter ($P = .02$), lateral ventricles, sulcal CSF and thalamus ($P < .001$), and nucleus caudatus and putamen ($P < .01$)	Iowa Longitudinal Study; 91% schizophrenia. Some but not all findings survive correction for multiple comparisons
[213]	84	116	3 y	Significantly greater decrease in patients concerning cerebral gray matter volume ($P = 0.006$) and cortical volume ($P = 0.03$) and thickness ($P = 0.02$). Patients showed additional loss in cortical volume and thickness of the right supramarginal, posterior superior temporal, left supramarginal, left postcentral, and occipital regions (P values between <.001 and .03 after clusterwise correction)	Results do not survive correction for multiple comparisons
[215]	51	13	1 y	Patients caudate nuclei volumes increased over time ($P = .0003$), but not of controls. Control subjects' anterior hippocampal volumes decreased over time ($P = .03$), but those of patients did not. The total cortical volumes decreased in controls but not in patients, and there was no differential change over time in the volumes of the lateral ventricles, total ventricles, and third ventricle. In poor outcome patients, the volume of the ventricles increases ($P = .0089$), and the hippocampal volumes increased ($P = .009$)	Except from the findings concerning the nucleus caudatus, the rest of the results do not survive correction for multiple comparisons
[231]	145 HR subjects; 21 developed schizophrenia	36	10 y	HR subjects had significantly greater reductions over time in terms of whole brain volume ($P < .001$), left and right temporal lobes ($P < .001$ and $P = .04$), and left prefrontal lobe ($P = .002$). Patients with schizophrenia showed greater tissue loss in both prefrontal lobes than the other HR subjects ($P = .02$)	Findings concerning HR subjects vs controls survive correction for multiple comparison but not those within the HR group; the results suggest the presence of an endophenotype
[233]	96	113	5 y	In patients, there were significant decreases in gray matter density in the left superior frontal area (Brodmann areas 9/10), left superior temporal gyrus (Brodmann area 42), right caudate nucleus, and right thalamus as compared to healthy individuals ($P < .05$; corrected)	The results were corrected for multiple comparisons
[212]	96	113	5 y	In patients, there was significant cortical thinning in bilaterally in the temporal cortex and in the left frontal area but also in other areas (all at $P < .001$). Poor outcome in patients was associated with more pronounced cortical thinning	Results would survive correction for multiple comparisons
[211]	33	71	9 y	There was a significant difference in the mean annual whole brain volume reduction (schiz: 0.69% vs controls: 0.49%; $P = .003$)	Northern Finland Birth Cohort 1966

Abbreviations: CSF, cerebrospinal fluid; DUP, duration of untreated psychosis; HR, high risk; HVI, hippocampal volumetric integrity.

Table 5B. Studies on the Long-Term Effect of Antipsychotic Treatment on the Progression of Structural Brain Changes in Patients with Schizophrenia

Study	Patients with Schizophrenia	Controls	Follow-up	Results	Comments
[236]	33	31	6-9 mo	All patients were under clozapine at follow-up. No difference at baseline or follow-up and no difference between responders and nonresponders	
[199]	202		7 y	Significant decrease in total brain volume ($P = .01$), and in frontal ($P = .02$) and temporal ($P = .03$) and parietal white matter ($P = .03$) volume in patients receiving antipsychotics	Iowa Longitudinal Study. Results do not survive correction for multiple comparisons
[214]	16	20	1 y	Patients on antipsychotics manifested a significant decrease in the volume of accumbens ($P = .04$) and the putamen ($P < .01$) in comparison to those who discontinued	Results do not survive correction for multiple comparisons
[173]	31	32	8 wk	Mean daily antipsychotic dose was not significantly associated with HVI	The study utilized a unique imaging method
[235]	119	—	3 y	No independent effect of antipsychotic treatment on brain volume loss. Higher dosage correlated with frontal gray matter loss ($P = .03$)	Iowa Longitudinal Study. Results do not survive correction for multiple comparisons
[234]	211	—	7 y	Antipsychotic dosage correlated to frontal temporal and parietal gray matter loss ($P < .05$) and putamen volume loss ($P < .001$)	Iowa Longitudinal Study; 91% schizophrenia. Only the finding concerning putamen volume would survive correction for multiple comparisons
[257]	164 (82 under olanzapine and 82 under haloperidol)	58	2 y	Significant difference in change in the nucleus caudatus volume at endpoint for the haloperidol-treated patients ($P = .04$)	Only two-thirds were suffering from schizophrenia. Results do not survive correction for multiple comparisons
[256]	19 (13 under risperidone or ziprasidone; 6 under haloperidol)	7	1 mo	Patients under risperidone and ziprasidone manifested a significant increase in cerebral cortical gray matter volume ($P < .0005$). The rest of patients and controls did not	Results would survive correction for multiple comparisons
[258]	52 (haloperidol: 18; risperidone: 16; olanzapine: 18)		1 y	Significant increase in lateral ventricles in patients treated with risperidone ($P = .009$), and decrease in caudate nucleus volume in patients under olanzapine and risperidone ($P = .001$)	Results would not survive correction for multiple comparisons
[233]	96	113	5 y	Clozapine and olanzapine treatment was significantly related to less decrease in density in the left superior frontal gyrus	The results were corrected for multiple comparisons
[211]	33	71	9 y	Cumulative exposure to antipsychotic medication predicted reduction in brain volume in patients ($P < .05$ after adjusting for symptom severity)	Results would not survive correction for multiple comparisons

Abbreviation: HVI, hippocampal volumetric integrity.

pathophysiology of the specific disease) they can cause harm, often in the same direction of the disease itself. Such an example is insulin, which protects diabetic patients from developing vascular dementia, but if given to normal people it could cause brain damage because of hypoglycaemia[252–254] especially if occurring abruptly.[255] Antihypertensive agents, hormone supplements, anticancer medication, and cortisol are among other examples with a similar effect.

Concerning human studies, some authors suggest a clear correlation after controlling for possible confounders between exposure to antipsychotics and brain volume loss,[234] others suggest correlations with increased or less decreased brain volume,[233,256] some studies did not find any relationship at all,[173,236] while others lose their strength after correction for multiple comparisons.[199,211,214,235,257,258]

A meta-analysis included 43 studies and structural data from 965 FEP subjects matched with 1040 controls and identified conjoint structural and functional differences in the insula/STG and the medial frontal/anterior cingulate cortex bilaterally, and related to antipsychotic exposure.[232] Another meta-analysis of 317 cross-sectional studies (N=9098) on volumetric brain alterations in both medicated and antipsychotic-naive patients included over 9000 patients and 33 of these studies were in antipsychotic-naive patients. In the medicated schizophrenia patients (N=8327)a decreased intracranial and total brain volume was found by 2.0% and 2.6%, respectively. Largest effect sizes were observed for gray matter structures, with effect sizes ranging from −0.22 to −0.58. These authors argue that the main difference between medicated and antipsychotic-naïve patients in comparison to controls concerned the caudate nucleus and the thalamus. However, in the sample of antipsychotic-naive patients, with reference to controls there were significant volume reductions in the caudate nucleus (patients N = 299 vs controls N = 422; $d = -0.38$, 95% CI = –0.54 to −0.23; $P < .001$) and thalamus (patients N = 152 vs controls N = 260; $d = -0.68$, 95% CI = –1.08 to −0.28; $P < .001$). In contrast, medicated patients did not differ from controls concerning the volume of the caudate nucleus (patients $N = 1101$ vs controls $N = 1154$; $d = -0.03$, 95% CI = –0.14 to 0.07; $P > .05$) or the volume of the thalamus (patients N = 1168 vs controls N = 1350; $d = -0.31$, 95% CI = –0.40 to −0.22; $P < .001$). In fact, the authors are correct only concerning the caudate nucleus since the 95% CIs of the thalamus results overlap. Antipsychotic-naïve patients had significantly smaller caudate nucleus volumes. White matter volume was decreased to a similar extent in both groups, while gray matter loss was less extensive in antipsychotic-naive patients. Gray matter reduction was associated with longer duration of illness and higher dose of antipsychotic medication at time of scanning. Therefore, brain loss in schizophrenia is related to a combination of (early) neurodevelopmental processes—reflected in intracranial volume reduction—as well as illness progression. Most of the observed significant results would survive correction for multiple comparisons.[219]

A recent meta-analysis that has received much attention[240] reported that antipsychotics are responsible for brain volume loss, but it identified only three randomized controlled trials comparing FGA and SGA treatment. These studies are included in Table 5.[256–258] The meta-analysis reported that for the 56 patients treated with FGAs, there was a significant change from baseline ($g = -0.34$, CI = –0.60 to −0.08, $P = 0.009$) while there was no such a difference concerning the 90 patients treated with SGAs ($g = -0.19$, CI = –0.39 to 0.05; $P > .05$). Thus, these authors concluded that FGAs are responsible for brain atrophy while SGAs are not.[240] Unfortunately, this conclusion is erroneous, because this analysis in pairs is not an appropriate way to analyze three groups; the correct way would be to analyze all three groups simultaneously and in that case no significant difference would emerge since the confidence intervals overlap.

Thus, although several systematic reviews and meta-analyses have reported that antipsychotic-treated patients with schizophrenia have smaller brain volumes than untreated patients,[240,259–262] this morphological difference cannot be taken as a proof of functional relevance. For example, gray matter reductions in first-episode patients receiving antipsychotics sometimes were associated with poorer outcome,[263] but also sometimes were not associated with poorer outcome,[264] and limited longitudinal data suggested that patients stopping antipsychotics have gray matter volume loss, whereas increases were found in patients continuing their antipsychotics.[214] Importantly, comparing a first-episode sample on antipsychotics vs off antipsychotics, patients on antipsychotics, consistently with the structural results of the meta-analyses, had lower gray matter volumes, but better cognition and better functional connectivity between the brain areas.[265] These data underscore that multimodal assessments are needed that combine structural and functional brain imaging as well as symptomatic, cognitive, and functional clinical outcomes in order to understand better the relationship between antipsychotic treatment and adverse or beneficial effects on the brain and its functions.

Taken together both animal and human studies, it is highly unlikely that antipsychotics cause loss of brain volume in patients with schizophrenia, and the correlation of such changes to antipsychotic exposure in naturalistic studies, when present, is most likely to be the result of confounding factors that determine the treatment strategy and lead to patient selection. Brain volume loss probably occurs in a subgroup of patients who are at a greater need for treatment and is not the consequence of treatment with antipsychotics. On the other hand, the data do imply the possible presence of a protective effect of antipsychotic treatment against brain volume loss (Table 5A,B).

Discussion

The current paper utilized a selective but comprehensive review of the literature and took into consideration the most relevant arguments developed during the last few years for or against the acute and long-term use of antipsychotics in people with schizophrenia. It is essential to evaluate these arguments into the frame of evidence-based medicine. More specifically, although the current paper did not utilize a systematic review as a proper evidence-based approach would do,[266] it articulated specific questions and tried to identify pro and con arguments in the literature,[267] utilizing a critical appraisal of the published evidence to identify potential errors, biases, and confounders.[268-270]

Eventually, this review arrived at a number of conclusions (Table 6) including that brain volume loss probably occurs in a subgroup of patients who are at greater need for treatment and is not the direct or adverse consequence of treatment with antipsychotics.

Overall, the data indicate that antipsychotic treatment is the only definitely proven method for the acute treatment and long-term prevention of psychotic episodes, and especially of schizophrenia. Antipsychotic use includes a number of dangers including tardive dyskinesia and the development of metabolic syndrome.[9,10,41,42,271–274] However, one need not take this risk into consideration and chose lowest-risk antipsychotics whenever possible,[37,38,40] but also put these adverse effects into the context of the risk on untreated illness. In this context, nationwide data are consistent and strong,

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Table 6. List of Questions and Answers

Question	Answer
1. Are antipsychotics efficacious during the acute psychotic phase?	There is wide consensus that antipsychotics are definitely efficacious during the acute phase
2. Should antipsychotics be used in first-episode patients?	Yes. It is impossible to predict which patients will remit without treatment and which of them do not suffer from schizophrenia
3. Is there an antipsychotics discontinuation/withdrawal effect? What about the dopamine super-sensitivity hypothesis?	Overall, there seems to be some sensitization of dopamine receptors at least in some patients, but this does not cause a rebound psychotic exacerbation if antipsychotics are stopped either abruptly or gradually and does not contribute to a worse global outcome in patients with schizophrenia
4. Does the initial treatment with antipsychotics worsens the long-term outcome?	The data do not suggest a deleterious effect of initial antipsychotic treatment; on the contrary there are at least some data suggesting a long-term beneficial effect
5. Does maintenance treatment with antipsychotics worsen the long-term outcome?	Maintenance treatment is related to a more favorable outcome in terms of relapse prevention and maybe lower mortality rates
6. Does the relapse rate level after 3 years irrespective of treatment?	After some time relapses are fewer in number but of longer duration and more refractory
7. Is long duration of untreated psychosis (DUP) toxic?	Longer DUP is modestly related to positive and negative symptoms as well as several indices reflecting functioning and remission both at baseline and after treatment and follow-up, but the effect on neurocognitive function is equivocal. The data on the possible neurotoxic effect are less robust
8. Are relapses toxic?	Overall relapses correlate with worse long-term outcome
9. Is there a brain volume loss in patients with schizophrenia? (at any stage)	The data are strong in suggesting that schizophrenia is characterized by loss of total gray matter volume which is probably more pronounced in the temporal lobes. It seems that a reduction in interneuronal neuropil in the prefrontal cortex is responsible for volume loss. These brain abnormalities seem to be present already at illness onset and progress at least in a subgroup of patients
10. Does antipsychotic treatment cause brain volume loss?	The data do not support that antipsychotics cause loss of brain volume in patients with schizophrenia. On the other hand, the data do not preclude the presence of a protective effect of antipsychotic treatment against brain volume loss

Abbreviation: DUP, duration of untreated psychosis.

suggesting that treatment with antipsychotics is related to lower mortality in comparison to no-medication treatment.[53–57]

As an aid to clinicians, expert opinion and guidelines offer specific advice on how best to treat patients with schizophrenia. Only the Canadian guidelines suggest that patients in symptomatic remission and functional recovery on antipsychotic medication for at least 1 to 2 years should be offered the option to discontinue antipsychotic treatment; the remaining 10 of 11 guidelines did not recommend discontinuation of antipsychotics within 5 years,[275] and this is in accord with the data reviewed above. Most likely, only patients with a psychotic episode who remitted symptomatically and recovered functionally and who do not fulfill the criteria for schizophrenia should be considered as candidates for medication discontinuation,[276] and some authors propose a shift to a low dosage especially after FEP[277] but others insist that prolonged maintenance treatment is essential for FEP[100] and life-long maintenance treatment is absolutely necessary for definite schizophrenia.[278]

The presence of brain structural abnormalities in patients with schizophrenia has been positioned at the center of the debate on antipsychotics. It is clear today that neurodevelopmentally related abnormalities do exist, and the causes include among others adverse obstetric events,[279–286] but some authors suggest that additional insults, which trigger stress-related mechanisms of response, are necessary.[287,288] These additional insults probably involve a dopamine dysregulation mechanism[287,289] as well as/including substance, especially cannabis abuse.[238] All these theories and proposals are open to discussion, and the available data are not conclusive concerning the etiopathogenesis of schizophrenia. The data are conclusive, however, concerning the answer to the question whether brain alterations exist independently of medication treatment. The data are less clear concerning the possible progressive nature of these changes, which seem to be present in a subgroup of patients and, based on the current evidence, appear to be unrelated to antipsychotic treatment in a causal way.

The review of the literature suggests that radically opposing opinions are frequently published in scientific journals, in spite of their weak background. One interesting and potentially dangerous feature of the ongoing debate on the usefulness or potential dangers of antipsychotic treatment for people with schizophrenia is that lay persons publish in scientific medical journals,[17] while on the other hand, letters by scholars not accepted for publication by scientific journals are published with an accusatory attitude in lay web sites.[163,182] This situation is not entirely new since it had happened in the 1940s and 1950s in the frame of the attack against electroconvulsive therapy (ECT) by William Menninger (1899-1966) and the later critics of ECT,[290] relating also to the stigma of psychiatric disorders and their treatments.

The results of this review have to be interpreted within its limitations. These include the selective and narrative nature of this review and consensus statement. Additional limitations of the data include lack of long-term randomized controlled trials lasting >3 years, the long list of selection factors in RCTs, lack of long-term studies with state-of-the-art biological marker and outcome tracking, and the current inability to parse patients with schizophrenia into meaningful biological and/or clinical subgroups, including the identification first-episode schizophrenia patients who will not suffer from a second psychotic episode. Furthermore, the effects of DUP on illness status at baseline and on longer term outcomes

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are related to confounders that need to be understood better. Finally, animal models for schizophrenia are insufficient, and brain morphological studies are influenced by often unmeasured confounders and largely lacked the assessment of brain functioning in the imaging and clinical outcome domains.

In summary, in this review concerning the risk/benefit ratio of antipsychotics in the treatment of schizophrenia, the joint WPA/-CINP workgroup members conclude that the currently available data strongly support the use of antipsychotics both during the acute and the maintenance phase without suggesting that it is wise to discontinue antipsychotics after a certain period of time, and that antipsychotic treatment improves long-term outcomes and lowers overall and specific-cause mortality.

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References

1. Kane JM, Correll CU. Past and present progress in the pharmacologic treatment of schizophrenia. *J Clin Psychiatry*. 2010;**71**(9):1115–1124.
2. Carlsson A, Lindqvist M. Effect of chlorpromazine or haloperidol on formation of 3methoxytyramine and normetanephrine in mouse brain. *Acta pharmacologica et toxicologica*. 1963;**20**:140–144.
3. van Rossum JM. The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Archives internationales de pharmacodynamie et de therapie*. 1966;**160**(2):492–494.
4. Carlsson A. Arvid Carlsson. In: Squire L, ed. *The History of Neuroscience in Autobiography*. Vol **2**. San Diego, CA: Academic Press; 1998:28–66.
5. Carlsson A. The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol Rev*. 1959;**11**(2, Part 2): 490–493.
6. Copolov D. New name for atypical antipsychotics? *Am J Psychiatry*. 1997; **154**(3):439.
7. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. *J Pharmacol Exp Ther*. 1989;**251**(1):238–246.
8. Leucht S, Leucht C, Huhn M, *et al.* Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, bayesian meta-analysis, and meta-regression of efficacy predictors. *Am J Psychiatry*. 2017;**174**(10):927–942.
9. Carbon M, Kane JM, Leucht S, Correll CU. Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psychiatry*. 2018;**17**(3):330–340.
10. Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. *J Clin Psychiatry*. 2017;**78**(3):e264–e278.
11. Kahn RS, Sommer IE, Murray RM, *et al.* Schizophrenia. *Nat Rev Dis Primers*. 2015;**1**:15067.
12. Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? *World Psychiatry*. 2018;**17**(2):149–160.
13. Leucht S, Heres S, Hamann J, Kane JM. Methodological issues in current antipsychotic drug trials. *Schizophr Bull*. 2008;**34**(2):275–285.
14. Buchanan RW, Kreyenbuhl J, Kelly DL, *et al.* The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;**36**(1):71–93.
15. Gotzsche PC, Young AH, Crace J. Does long term use of psychiatric drugs cause more harm than good? *BMJ*. 2015;**350**:h2435
16. Moncrieff J. Antipsychotic maintenance treatment: time to rethink? *PLoS Med*. 2015;**12**(8):e1001861.
17. Whitaker R. The case against antipsychotic drugs: a 50-year record of doing more harm than good. *Med Hypotheses*. 2004;**62**(1):5–13.
18. Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry*. 2013;**70** (9):913–920.
19. Rappaport M, Hopkins HK, Hall K, Belleza T, Silverman J. Are there schizophrenics for whom drugs may be unnecessary or contraindicated? *Int Pharmacopsychiatry*. 1978;**13**(2):100–111.
20. Calton T, Ferriter M, Huband N, Spandler H. A systematic review of the Soteria paradigm for the treatment of people diagnosed with schizophrenia. *Schizophr Bull*. 2008;**34**(1):181–192.
21. Moncrieff J. Inconvenient truths about antipsychotics: a response to Goff et al. *Mad in America*. May 7, 2017. https://www.madinamerica.com/2017/05/inconvenient-truths-about-antipsychotics-a-response-to-goff-et-al/. Accessed July 5, 2018.
22. Murray RM, Quattrone D, Natesan S, *et al.* Should psychiatrists be more cautious about the long-term prophylactic use of antipsychotics? *Br J Psychiatry*. 2016;**209**(5):361–365.
23. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev*. 2012;(5):CD008016
24. Leucht S, Cipriani A, Spineli L, *et al.* Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;**382**(9896):951–962.
25. Leucht S, Kissling W, Davis JM. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? *Psychol Med*. 2009;**39**(10): 1591–1602.
26. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res*. 1999;**35**(1):51–68.
27. Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Mol Psychiatry*. 2009;**14**(4):429–447.

https://doi.org/10.1017/S1092852920001546 Published online by Cambridge University Press

28. Haddad PM, Correll CU. The acute efficacy of antipsychotics in schizophrenia: a review of recent meta-analyses. *Ther Adv Psychopharmacol*. 2018;**8**(11):303–318.
29. Zhu Y, Krause M, Huhn M, *et al.* Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. *Lancet Psychiatry*. 2017; **4**(9):694–705.
30. Samara MT, Nikolakopoulou A, Salanti G, Leucht S. How many patients with schizophrenia do not respond to antipsychotic drugs in the short term? An Analysis Based on individual patient data from randomized controlled trials. *Schizophr Bull*. 2019;**45**(3):639–646.
31. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. *Br J Psychiatry*. 2012;**200**(2):97–106.
32. Kishimoto T, Hagi K, Nitta M, Kane JM, Correll CU. Long-term effectiveness of oral second-generation antipsychotics in patients with schizophrenia and related disorders: a systematic review and meta-analysis of direct head-to-head comparisons. *World Psychiatry*. 2019;**18**(2):208–224.
33. Fusar-Poli P, Papanastasiou E, Stahl D, *et al.* Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. *Schizophr Bull*. 2015;**41**(4):892–899.
34. Goldberg TE, Goldman RS, Burdick KE, *et al.* Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry*. 2007;**64** (10):1115–1122.
35. Mishara AL, Goldberg TE. A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. *Biol Psychiatry*. 2004;**55**(10):1013–1022.
36. Nielsen RE, Levander S, Kjaersdam Telleus G, Jensen SO, Ostergaard Christensen T, Leucht S. Second-generation antipsychotic effect on cognition in patients with schizophrenia—a meta-analysis of randomized clinical trials. *Acta Psychiatr Scand*. 2015;**131**(3):185–196.
37. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry*. 2015;**14**(2):119–136.
38. Huhn M, Nikolakopoulou A, Schneider-Thoma J, *et al.* Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;**394**(10202):939–951.
39. Schneider-Thoma J, Efthimiou O, Bighelli I, *et al.* Second-generation antipsychotic drugs and short-term somatic serious adverse events: a systematic review and meta-analysis. *Lancet Psychiatry*. 2019;**6**(9): 753–765.
40. Solmi M, Murru A, Pacchiarotti I, *et al.* Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. *Ther Clin Risk Manag*. 2017;**13**:757–777.
41. Galling B, Roldan A, Nielsen RE, *et al.* Type 2 diabetes mellitus in youth exposed to antipsychotics: a systematic review and meta-analysis. *JAMA Psychiatry*. 2016;**73**(3):247–259.
42. Vancampfort D, Correll CU, Galling B, *et al.* Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry*. 2016; **15**(2):166–174.
43. Vancampfort D, Stubbs B, Mitchell AJ, *et al.* Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry*. 2015;**14**(3):339–347.
44. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. 2009;**360**(3): 225–235.
45. Correll CU, Solmi M, Veronese N, *et al.* Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry*. 2017;**16**(2):163–180.
46. Firth J, Siddiqi N, Koyanagi A, *et al.* The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry*. 2019;**6**(8):675–712.
47. Ifteni P, Correll CU, Burtea V, Kane JM, Manu P. Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients. *Schizophr Res*. 2014;**155**(1–3):72–76.
48. Manu P, Kane JM, Correll CU. Sudden deaths in psychiatric patients. *J Clin Psychiatry*. 2011;**72**(7):936–941.
49. Stubbs B, Koyanagi A, Veronese N, *et al.* Physical multimorbidity and psychosis: comprehensive cross sectional analysis including 242,952 people across 48 low- and middle-income countries. *BMC Med*. 2016;**14**(1): 189.
50. Stubbs B, Vancampfort D, Hallgren M, *et al.* EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and position statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). *Eur Psychiatry*. 2018;**54**: 124–144.
51. Papola D, Ostuzzi G, Gastaldon C, *et al.* Antipsychotic use and risk of life-threatening medical events: umbrella review of observational studies. *Acta Psychiatr Scand*. 2019;**140**(3):227–243.
52. Yang C, Hao Z, Tian J, *et al.* Does antipsychotic drug use increase the risk of long term mortality? A systematic review and meta-analysis of observational studies. *Oncotarget*. 2018;**9**(19):15101–15110.
53. Taipale H, Mittendorfer-Rutz E, Alexanderson K, *et al.* Antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia. *Schizophr Res*. 2018;**197**:274–280.
54. Taipale H, Tanskanen A, Mehtala J, Vattulainen P, Correll CU, Tiihonen J. 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry*. 2020;**19**(1):61–68.
55. Tiihonen J, Mittendorfer-Rutz E, Torniainen M, Alexanderson K, Tanskanen A. Mortality and cumulative exposure to antipsychotics, antidepressants, and benzodiazepines in patients with schizophrenia: an observational follow-up study. *Am J Psychiatry*. 2016;**173**(6):600–606.
56. Torniainen M, Mittendorfer-Rutz E, Tanskanen A, *et al.* Antipsychotic treatment and mortality in schizophrenia. *Schizophr Bull*. 2015;**41**(3): 656–663.
57. Vermeulen JM, van Rooijen G, van de Kerkhof MPJ, Sutterland AL, Correll CU, de Haan L. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1-12.5 years. *Schizophr Bull*. 2019;**45**(2):315–329.
58. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*. 2013;**16**(6):1205–1218.
59. Lally J, Ajnakina O, Di Forti M, *et al.* Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychol Med*. 2016;**46**(15):3231–3240.
60. Kane JM, Agid O, Baldwin ML, *et al.* Clinical guidance on the identification and management of treatment-resistant schizophrenia. *J Clin Psychiatry*. 2019;**80**(2):
61. Bola JR, Lehtinen K, Aaltonen J, Rakkolainen V, Syvalahti E, Lehtinen V. Predicting medication-free treatment response in acute psychosis: cross-validation from the Finnish Need-Adapted Project. *J Nerv Ment Dis*. 2006; **194**(10):732–739.
62. Huber G, Gross G, Schuttler R, Linz M. Longitudinal studies of schizophrenic patients. *Schizophr Bull*. 1980;**6**(4):592–605.
63. Emsley R, Chiliza B, Asmal L, *et al.* A randomized, controlled trial of omega-3 fatty acids plus an antioxidant for relapse prevention after antipsychotic discontinuation in first-episode schizophrenia. *Schizophr Res*. 2014;**158**(1–3):230–235.
64. Emsley R, Oosthuizen P, Koen L, Niehaus D, Martinez L. Comparison of treatment response in second-episode versus first-episode schizophrenia. *J Clin Psychopharmacol*. 2013;**33**(1):80–83.
65. Takeuchi H, Siu C, Remington G, *et al.* Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. second-episode schizophrenia. *Neuropsychopharmacology*. 2019;**44**(6):1036–1042.
66. Zipursky RB, Menezes NM, Streiner DL. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. *Schizophr Res*. 2014;**152**(2–3):408–414.

67. Addington J, Cornblatt BA, Cadenhead KS, *et al.* At clinical high risk for psychosis: outcome for nonconverters. *Am J Psychiatry*. 2011;**168**(8): 800–805.
68. Rabinowitz J, Reichenberg A, Weiser M, Mark M, Kaplan Z, Davidson M. Cognitive and behavioural functioning in men with schizophrenia both before and shortly after first admission to hospital. Cross-sectional analysis. *Br J Psychiatry*. 2000;**177**:26–32.
69. Reichenberg A, Weiser M, Rapp MA, *et al.* Elaboration on premorbid intellectual performance in schizophrenia: premorbid intellectual decline and risk for schizophrenia. *Arch Gen Psychiatry*. 2005;**62**(12):1297–1304.
70. Zhang T, Xu L, Tang X, *et al.* Real-world effectiveness of antipsychotic treatment in psychosis prevention in a 3-year cohort of 517 individuals at clinical high risk from the SHARP (ShangHai At Risk for Psychosis). *Aust N Z J Psychiatry*. 2020;**54**:696–706.
71. Bosnjak Kuharic D, Kekin I, Hew J, Rojnic Kuzman M, Puljak L. Interventions for prodromal stage of psychosis. *Cochrane Database Syst Rev*. 2019;**2019**(11):CD012236.
72. Yung AR, Phillips LJ, Nelson B, *et al.* Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. *J Clin Psychiatry*. 2011;**72**(4):430–440.
73. Lee TY, Kim SN, Correll CU, *et al.* Symptomatic and functional remission of subjects at clinical high risk for psychosis: a 2-year naturalistic observational study. *Schizophr Res*. 2014;**156**(2–3):266–271.
74. Liu CC, Chien YL, Hsieh MH, Hwang TJ, Hwu HG, Liu CM. Aripiprazole for drug-naive or antipsychotic-short-exposure subjects with ultra-high risk state and first-episode psychosis: an open-label study. *J Clin Psychopharmacol*. 2013;**33**(1):18–23.
75. Kelly C, Hadjinicolaou AV, Holt C, Agius M, Zaman R. Meta-analysis of medical and non-medical treatments of the prodromal phase of psychotic illness in at-risk mental states. *Psychiatr Danub*. 2010;**22**(suppl 1): S56–S62.
76. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry*. 1991;**148**(11): 1474–1486.
77. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol*. 2015;**29**(2): 97–115.
78. Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol*. 2001;**41**(1): 237–260.
79. Grace AA. Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Res Brain Res Rev*. 2000;**31**(2–3): 330–341.
80. Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S. Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: insights from PET and SPECT imaging. *Curr Pharm Des*. 2009;**15**(22):2550–2559.
81. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull*. 2009;**35**(3):549–562.
82. Nordstrom AL, Farde L, Wiesel FA, *et al.* Central D2-dopamine receptor occupancy in relation to antipsychotic drug effects: a double-blind PET study of schizophrenic patients. *Biol Psychiatry*. 1993;**33**(4):227–235.
83. Boter H, Peuskens J, Libiger J, *et al.* Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). *Schizophr Res*. 2009;**115**(2–3):97–103.
84. Samaha AN, Seeman P, Stewart J, Rajabi H, Kapur S. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *J Neurosci*. 2007;**27**(11):2979–2986.
85. Ginovart N, Wilson AA, Hussey D, Houle S, Kapur S. D2-receptor upregulation is dependent upon temporal course of D2-occupancy: a longitudinal [11C]-raclopride PET study in cats. *Neuropsychopharmacology*. 2009;**34**(3):662–671.
86. Weidenauer A, Bauer M, Bartova L, *et al.* Behavioral measures of sensitization to repeated d-amphetamine: preliminary data on sex differences in healthy humans. *Eur Neuropsychopharmacol*. 2016;**26**:S265–S265.
87. Muller P, Seeman P. Brain neurotransmitter receptors after long-term haloperidol: dopamine, acetylcholine, serotonin, alpha-noradrenergic and naloxone receptors. *Life Sci*. 1977;**21**(12):1751–1758.
88. Moller Nielsen I, Fjalland B, Pedersen V, Nymark M. Pharmacology of neuroleptics upon repeated administration. *Psychopharmacologia*. 1974; **34**(2):95–104.
89. Prien RF, Levine J, Switalski RW. Discontinuation of chemotherapy for chronic schizophrenics. *Hosp Community Psychiatry*. 1971;**22**(1):4–7.
90. Schooler NR, Goldberg SC, Boothe H, Cole JO. One year after discharge: community adjustment of schizophrenic patients. *Am J Psychiatry*. 1967; **123**(8):986–995.
91. Marsden CD. Cerebral atrophy and cognitive impairment in chronic schizophrenia. *Lancet*. 1976;**308**(7994):1079
92. Rupniak MN, Jenner P, Marsden CD. The effect of chronic neuroleptic administration on cerebral dopamine receptor function. *Life Sci*. 1983;**32** (20):2289–2311.
93. Chouinard G. Severe cases of neuroleptic-induced supersensitivity psychosis. Diagnostic criteria for the disorder and its treatment. *Schizophr Res*. 1991;**5**(1):21–33.
94. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. *Am J Psychiatry*. 1980;**137**(1): 16–21.
95. Chouinard G, Jones BD, Annable L. Neuroleptic-induced supersensitivity psychosis. *Am J Psychiatry*. 1978;**135**(11):1409–1410.
96. Gitlin M, Nuechterlein K, Subotnik KL, *et al.* Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiatry*. 2001;**158**(11):1835–1842.
97. Takeuchi H, Kantor N, Sanches M, Fervaha G, Agid O, Remington G. One-year symptom trajectories in patients with stable schizophrenia maintained on antipsychotics versus placebo: meta-analysis. *Br J Psychiatry*. 2017;**211**(3):137–143.
98. Viguera AC, Baldessarini RJ, Hegarty JD, van Kammen DP, Tohen M. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. *Arch Gen Psychiatry*. 1997;**54**(1):49–55.
99. Leucht S, Tardy M, Komossa K, *et al.* Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;**379**(9831):2063–2071.
100. Tiihonen J, Tanskanen A, Taipale H. 20-year nationwide follow-up study on discontinuation of antipsychotic treatment in first-episode schizophrenia. *Am J Psychiatry*. 2018;**175**(8):765–773.
101. Rubio JM, Taipale H, Correll CU, Tanskanen A, Kane JM, Tiihonen J. Psychosis breakthrough on antipsychotic maintenance: results from a nationwide study. *Psychol Med*. 2020;**50**:1356–1367.
102. Emsley R, Asmal L, Rubio JM, Correll CU, Kane JM. Predictors of psychosis breakthrough during 24 months of long-acting antipsychotic maintenance treatment in first episode schizophrenia. *Schizophr Res*. 2019;
103. Chiappini S, Schifano F, Corkery JM, Guirguis A. Focus on clozapine withdrawal- and misuse-related cases as reported to the European Medicines Agency (EMA) pharmacovigilance database. *Brain Sci*. 2020;**10**(2): 105.
104. Bastiampillai T, Juneja V, Nance MJ. Clozapine rebound mania. *Aust N Z J Psychiatry*. 2014;**48**(1):98–99.
105. Stanilla JK, de Leon J, Simpson GM. Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. *J Clin Psychiatry*. 1997;**58** (6):252–255.
106. Stevenson E, Schembri F, Green DM, Burns JD. Serotonin syndrome associated with clozapine withdrawal. *JAMA Neurol*. 2013;**70**(8): 1054–1055.
107. Bilbily J, McCollum B, de Leon J. Catatonia secondary to sudden clozapine withdrawal: a case with three repeated episodes and a literature review. *Case Rep Psychiatry*. 2017;**2017**:2402731.
108. Boazak M, Cotes RO, Potvin H, Decker AM, Schwartz AC. Catatonia due to clozapine withdrawal: a case report and literature review. *Psychosomatics*. 2019;**60**(4):421–427.
109. Kumar S, Sur S, Singh A. Catatonia following abrupt stoppage of clozapine. *Aust N Z J Psychiatry*. 2011;**45**(6):499

https://doi.org/10.1017/S1092852920001546 Published online by Cambridge University Press

110. Margetic B, Aukst-Margetic B. Neuroleptic malignant syndrome and clozapine withdrawal at the same time? *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;**29**(1):145–147.
111. Hazari N, Kate N, Grover S. Clozapine and tardive movement disorders: a review. *Asian J Psychiatr*. 2013;**6**(6):439–451.
112. Ahmed S, Chengappa KN, Naidu VR, Baker RW, Parepally H, Schooler NR. Clozapine withdrawal-emergent dystonias and dyskinesias: a case series. *J Clin Psychiatry*. 1998;**59**(9):472–477.
113. Galova A, Berney P, Desmeules J, Sergentanis I, Besson M. A case report of cholinergic rebound syndrome following abrupt low-dose clozapine discontinuation in a patient with type I bipolar affective disorder. *BMC Psychiatry*. 2019;**19**(1):73
114. Sarma S, Chetia D, Raha B, Agarwal G. Clozapine withdrawal emergent dystonia, oculogyric crisis and rebound psychosis in a single patient. *Ther Adv Psychopharmacol*. 2016;**6**(2):145–146.
115. Carpenter WT, McGlashan TH, Strauss JS. The treatment of acute schizophrenia without drugs: an investigation of some current assumptions. *Am J Psychiatry*. 1977;**134**(1):14–20.
116. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scand*. 2006;**114**(1):3–13.
117. Goff DC, Falkai P, Fleischhacker WW, *et al.* The long-term effects of antipsychotic medication on clinical course in schizophrenia. *Am J Psychiatry*. 2017;**174**(9):840–849.
118. Francey SM, Nelson B, Thompson A, *et al.* Who needs antipsychotic medication in the earliest stages of psychosis? A reconsideration of benefits, risks, neurobiology and ethics in the era of early intervention. *Schizophr Res*. 2010;**119**(1–3):1–10.
119. Sohler N, Adams BG, Barnes DM, Cohen GH, Prins SJ, Schwartz S. Weighing the evidence for harm from long-term treatment with antipsychotic medications: a systematic review. *Am J Orthopsychiatry*. 2016;**86**(5):477–485.
120. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. *Schizophr Bull*. 1991;**17**(2):325–351.
121. May PR, Tuma AH, Yale C, Potepan P, Dixon WJ. Schizophrenia—a follow-up study of results of treatment. *Arch Gen Psychiatry*. 1976;**33**(4):481–486.
122. McWalter HS, Mercer R, Sutherland M, Watt A. Outcomes of treatment of schizophrenia in a north-east Scottish mental hospital. *Am J Psychiat*. 1961;**118**(6):529–533.
123. Odegard O. Pattern of discharge from Norwegian psychiatric hospitals before and after the introduction of the psychotropic drugs. *Am J Psychiatry*. 1964;**120**(8):772–778.
124. Peterson DB, Olson GW. First admitted schizophrenics in drug era; follow-up Anoka schizophrenic cohort, 1956-1958. *Arch Gen Psychiatry*. 1964;**11**(2):137–144.
125. Pritchard M. Prognosis of schizophrenia before and after pharmacotherapy: I. Short term outcome. *Br J Psychiatry*. 1967;**113**(505):1345–1352.
126. Zhou Y, Li G, Li D, Cui H, Ning Y. Dose reduction of risperidone and olanzapine can improve cognitive function and negative symptoms in stable schizophrenic patients: a single-blinded, 52-week, randomized controlled study. *J Psychopharmacol*. 2018;**32**(5):524–532.
127. Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Schizophr Res*. 1993;**9**(2–3):134
128. Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry*. 1994;**151**(10):1409–1416.
129. Jaaskelainen E, Juola P, Hirvonen N, *et al.* A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull*. 2013;**39**(6):1296–1306.
130. Alem A, Kebede D, Fekadu A, *et al.* Clinical course and outcome of schizophrenia in a predominantly treatment-naive cohort in rural Ethiopia. *Schizophr Bull*. 2009;**35**(3):646–654.
131. Kurihara T, Kato M, Reverger R, Tirta IGR, Kashima H. Never-treated patients with schizophrenia in the developing country of Bali. *Schizophr Res*. 2005;**79**(2–3):307–313.
132. Ran MS, Weng X, Chan CL, *et al.* Different outcomes of never-treated and treated patients with schizophrenia: 14-year follow-up study in rural China. *Br J Psychiatry*. 2015;**207**(6):495–500.
133. Padmavathi R, Rajkumar S, Srinivasan TN. Schizophrenic patients who were never treated--a study in an Indian urban community. *Psychol Med*. 1998;**28**(5):1113–1117.
134. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry*. 2007;**68**(5):654–661.
135. Gaebel W, Riesbeck M, Wolwer W, *et al.* Predictors for symptom re-exacerbation after targeted stepwise drug discontinuation in first-episode schizophrenia: results of the first-episode study within the German Research Network on Schizophrenia. *Schizophr Res*. 2016;**170**(1):168–176.
136. Gaebel W, Riesbeck M, Wolwer W, *et al.* Relapse prevention in first-episode schizophrenia—maintenance vs intermittent drug treatment with prodrome-based early intervention: results of a randomized controlled trial within the German Research Network on Schizophrenia. *J Clin Psychiatry*. 2011;**72**(2):205–218.
137. Cheung HK. Schizophrenics fully remitted on neuroleptics for 3-5 years—to stop or continue drugs? *Br J Psychiatry*. 1981;**138**:490–494.
138. Sampath G, Shah A, Krska J, Soni SD. Neuroleptic discontinuation in the very stable schizophrenic patient: relapse rates and serum neuroleptic levels. *Hum Psychopharmacol*. 1992;**7**(4):255–264.
139. Fenton WS, McGlashan TH. Sustained remission in drug-free schizophrenic patients. *Am J Psychiatry*. 1987;**144**(10):1306–1309.
140. Harrison G, Hopper K, Craig T, *et al.* Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry*. 2001;**178**(06):506–517.
141. Harrow M, Grossman LS, Jobe TH, Herbener ES. Do patients with schizophrenia ever show periods of recovery? A 15-year multi-follow-up study. *Schizophr Bull*. 2005;**31**(3):723–734.
142. Harrow M, Jobe TH, Faull RN. Do all schizophrenia patients need antipsychotic treatment continuously throughout their lifetime? A 20-year longitudinal study. *Psychol Med*. 2012;**42**(10):2145–2155.
143. Harrow M, Jobe TH, Faull RN. Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis? A 20-year multi-follow-up study. *Psychol Med*. 2014;**44**(14):3007–3016.
144. Harrow M, Jobe TH, Faull RN, Yang J. A 20-year multi-followup longitudinal study assessing whether antipsychotic medications contribute to work functioning in schizophrenia. *Psychiatry Res*. 2017;**256**:267–274.
145. Hui CLM, Honer WG, Lee EHM, *et al.* Long-term effects of discontinuation from antipsychotic maintenance following first-episode schizophrenia and related disorders: a 10 year follow-up of a randomised, double-blind trial. *Lancet Psychiatry*. 2018;**5**(5):432–442.
146. Kotov R, Fochtmann L, Li K, *et al.* Declining clinical course of psychotic disorders over the two decades following first hospitalization: evidence from the Suffolk County Mental Health Project. *Am J Psychiatry*. 2017;**174**(11):1064–1074.
147. Leff J, Sartorius N, Jablensky A, Korten A, Ernberg G. The International Pilot Study of Schizophrenia: five-year follow-up findings. *Psychol Med*. 1992;**22**(1):131–145.
148. Moilanen J, Haapea M, Miettunen J, *et al.* Characteristics of subjects with schizophrenia spectrum disorder with and without antipsychotic medication—a 10-year follow-up of the Northern Finland 1966 Birth Cohort study. *Eur Psychiatry*. 2013;**28**(1):53–58.
149. Morgan C, Lappin J, Heslin M, *et al.* Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. *Psychol Med*. 2014;**44**(13):2713–2726.
150. Revier CJ, Reininghaus U, Dutta R, *et al.* Ten-year outcomes of first-episode psychoses in the MRC AESOP-10 Study. *J Nerv Ment Dis*. 2015;**203**(5):379–386.
151. Tiihonen J, Wahlbeck K, Lonnqvist J, *et al.* Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ*. 2006;**333**(7561):224

152. Tiihonen J, Lonnqvist J, Wahlbeck K, *et al.* 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;**374**(9690):620–627.
153. Wils RS, Gotfredsen DR, Hjorthoj C, *et al.* Antipsychotic medication and remission of psychotic symptoms 10years after a first-episode psychosis. *Schizophr Res*. 2017;**182**:42–48.
154. Sampson S, Mansour M, Maayan N, Soares-Weiser K, Adams CE. Intermittent drug techniques for schizophrenia. *Cochrane Database Syst Rev*. 2013;20(7):CD006196.
155. World Health Organization. *Schizophrenia: An International Follow Up Study*. Chichester: John Wiley & Sons; 1979.
156. Cohen A, Patel V, Thara R, Gureje O. Questioning an axiom: better prognosis for schizophrenia in the developing world? *Schizophr Bull*. 2008;**34**(2):229–244.
157. Karagianis J, Novick D, Pecenak J, *et al.* Worldwide-Schizophrenia Outpatient Health Outcomes (W-SOHO): baseline characteristics of pan-regional observational data from more than 17,000 patients. *Int J Clin Pract*. 2009;**63**(11):1578–1588.
158. Kulhara P, Shah R, Grover S. Is the course and outcome of schizophrenia better in the 'developing' world? *Asian J Psychiatr*. 2009;**2**(2):55–62.
159. Padma TV. Developing countries: the outcomes paradox. *Nature*. 2014; **508**(7494):S14–S15.
160. Harrow M, Jobe TH. Long-term antipsychotic treatment of schizophrenia: does it help or hurt over a 20-year period? *World Psychiatry*. 2018;**17**(2): 162–163.
161. De Hert M, Correll CU, Cohen D. Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study. *Schizophr Res*. 2010;**117**(1):68–74.
162. Steingard S. Duration of untreated psychosis revisited: response to the Goff Paper. *Mad in America*. November 13, 2017. https://www.madinamerica.com/2017/11/duration-of-untreated-psychosis-response-goff-paper/. Accessed July 5, 2018.
163. Whitaker R. Thou shall not criticize our drugs. *Mad in America*. September 22, 2017. https://www.madinamerica.com/2017/09/thou-shall-not-criticize-our-drugs/. Accessed July 5, 2018.
164. Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med*. 2006;**36** (10):1349–1362.
165. Austin SF, Mors O, Budtz-Jorgensen E, *et al.* Long-term trajectories of positive and negative symptoms in first episode psychosis: a 10year follow-up study in the OPUS cohort. *Schizophr Res*. 2015;**168**(1–2):84–91.
166. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry*. 2005;**62**(9):975–983.
167. Penttila M, Jaaskelainen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2014;**205** (2):88–94.
168. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry*. 2005;**162**(10): 1785–1804.
169. Addington J, Van Mastrigt S, Addington D. Duration of untreated psychosis: impact on 2-year outcome. *Psychol Med*. 2004;**34**(2):277–284.
170. Albert N, Melau M, Jensen H, Hastrup LH, Hjorthoj C, Nordentoft M. The effect of duration of untreated psychosis and treatment delay on the outcomes of prolonged early intervention in psychotic disorders. *NPJ Schizophr*. 2017;**3**(1):34
171. Barnes TR, Leeson VC, Mutsatsa SH, Watt HC, Hutton SB, Joyce EM. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. *Br J Psychiatry*. 2008;**193**(3): 203–209.
172. Bottlender R, Sato T, Jager M, Groll C, Strauss A, Moller HJ. The impact of duration of untreated psychosis and premorbid functioning on outcome of first inpatient treatment in schizophrenic and schizoaffective patients. *Eur Arch Psychiatry Clin Neurosci*. 2002;**252**(5):226–231.
173. Goff DC, Zeng B, Ardekani BA, *et al.* Association of hippocampal atrophy with duration of untreated psychosis and molecular biomarkers during initial antipsychotic treatment of first-episode psychosis. *JAMA Psychiatry*. 2018;**75**(4):370–378.
174. Guo X, Li J, Wei Q, *et al.* Duration of untreated psychosis is associated with temporal and occipitotemporal gray matter volume decrease in treatment naive schizophrenia. *PLoS One*. 2013;**8**(12):e83679
175. Hegelstad WT, Larsen TK, Auestad B, *et al.* Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. *Am J Psychiatry*. 2012;**169**(4):374–380.
176. Ho BC, Alicata D, Ward J, *et al.* Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. *Am J Psychiatry*. 2003;**160**(1):142–148.
177. Melle I, Larsen TK, Haahr U, *et al.* Prevention of negative symptom psychopathologies in first-episode schizophrenia: two-year effects of reducing the duration of untreated psychosis. *Arch Gen Psychiatry*. 2008;**65**(6):634–640.
178. Primavera D, Bandecchi C, Lepori T, Sanna L, Nicotra E, Carpiniello B. Does duration of untreated psychosis predict very long term outcome of schizophrenic disorders? Results of a retrospective study. *Ann Gen Psychiatry*. 2012;**11**(1):21
179. Qin H, Zhang J, Wang Z, *et al.* Duration of untreated psychosis and clinical outcomes of first-episode schizophrenia: a 4-year follow-up study. *Shanghai Arch Psychiatry*. 2014;**26**(1):42–48.
180. Ran MS, Xiao Y, Chui CHK, *et al.* Duration of untreated psychosis (DUP) and outcome of people with schizophrenia in rural China: 14-year follow-up study. *Psychiatry Res*. 2018;**267**:340–345.
181. Sullivan SA, Carroll R, Peters TJ, *et al.* Duration of untreated psychosis and clinical outcomes of first episode psychosis: an observational and an instrumental variables analysis. *Early Interv Psychiatry*. 2019;**13**(4): 841–847.
182. Gøtzsche P. Psychiatry ignores an elephant in the room. *Mad in America*. September 21, 2017. https://www.madinamerica.com/2017/09/psychiatry-ignores-elephant-room/. Accessed July 5, 2018.
183. Melle I, Olav Johannesen J, Haahr UH, *et al.* Causes and predictors of premature death in first-episode schizophrenia spectrum disorders. *World Psychiatry*. 2017;**16**(2):217–218.
184. Bora E, Yalincetin B, Akdede BB, Alptekin K. Duration of untreated psychosis and neurocognition in first-episode psychosis: a meta-analysis. *Schizophr Res*. 2018;**193**:3–10.
185. Anderson KK, Rodrigues M, Mann K, *et al.* Minimal evidence that untreated psychosis damages brain structures: a systematic review. *Schizophr Res*. 2015;**162**(1–3):222–233.
186. Jonas KG, Fochtmann LJ, Perlman G, *et al.* Lead-time bias confounds association between duration of untreated psychosis and illness course in schizophrenia. *Am J Psychiatry*. 2020;**177**(4):327–334.
187. Fountoulakis KN, Dragioti E, Theofilidis AT, *et al.* Staging of schizophrenia with the use of PANSS: an international multi-center study. *Int J Neuropsychopharmacol*. 2019;**22**(11):681–697.
188. Robinson D, Woerner MG, Alvir JM, *et al.* Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;**56**(3):241–247.
189. Lieberman J, Jody D, Geisler S, *et al.* Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiatry*. 1993;**50**(5):369–376.
190. Lieberman JA, Alvir JM, Koreen A, *et al.* Psychobiologic correlates of treatment response in schizophrenia. *Neuropsychopharmacology*. 1996;**14** (3 suppl):13S–21S.
191. Wyatt RJ. Research in schizophrenia and the discontinuation of antipsychotic medications. *Schizophr Bull*. 1997;**23**(1):3–9.
192. Emsley R, Oosthuizen PP, Koen L, Niehaus DJ, Martinez G. Symptom recurrence following intermittent treatment in first-episode schizophrenia successfully treated for 2 years: a 3-year open-label clinical study. *J Clin Psychiatry*. 2012;**73**(4):e541–e547.
193. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. *Arch Gen Psychiatry*. 1991;**48**(8):739–745.

194. Birchwood M, Smith J, Macmillan F, *et al.* Predicting relapse in schizophrenia: the development and implementation of an early signs monitoring system using patients and families as observers, a preliminary investigation. *Psychol Med*. 1989;**19**(3):649–656.
195. Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull*. 1998;**24**(1):75–85.
196. Emsley R, Nuamah I, Hough D, Gopal S. Treatment response after relapse in a placebo-controlled maintenance trial in schizophrenia. *Schizophr Res*. 2012;**138**(1):29–34.
197. Carbon M, Correll CU. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. *Dialogues Clin Neurosci*. 2014;**16**(4): 505–524.
198. Curson DA, Barnes TR, Bamber RW, Platt SD, Hirsch SR, Duffy JC. Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial. III. Relapse postponement or relapse prevention? The implications for long-term outcome. *Br J Psychiatry*. 1985;**146**(5):474–480.
199. Andreasen NC, Liu D, Ziebell S, Vora A, Ho BC. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. *Am J Psychiatry*. 2013;**170**(6):609–615.
200. Cannon M, Jones P, Huttunen MO, *et al.* School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. *Arch Gen Psychiatry*. 1999;**56**(5):457–463.
201. Fuller R, Nopoulos P, Arndt S, O'Leary D, Ho BC, Andreasen NC. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *Am J Psychiatry*. 2002;**159**(7):1183–1189.
202. McGlashan TH. Is active psychosis neurotoxic? *Schizophr Bull*. 2006;**32** (4):609–613.
203. AlAqeel B, Margolese HC. Remission in schizophrenia: critical and systematic review. *Harv Rev Psychiatry*. 2012;**20**(6):281–297.
204. de Haan L, Nimwegen L, Amelsvoort T, Dingemans P, Linszen D. Improvement of subjective well-being and enduring symptomatic remission, a 5-year follow-up of first episode schizophrenia. *Pharmacopsychiatry*. 2008;**41**(4):125–128.
205. Kelly DL, Weiner E, Ball MP, McMahon RP, Carpenter WT, Buchanan RW. Remission in schizophrenia: the relationship to baseline symptoms and changes in symptom domains during a one-year study. *J Psychopharmacol*. 2009;**23**(4):436–441.
206. Emsley R, Rabinowitz J, Medori R, Early Psychosis Global Working Group. Remission in early psychosis: rates, predictors, and clinical and functional outcome correlates. *Schizophr Res*. 2007;**89**(1–3):129–139.
207. Zhu Y, Li C, Huhn M, *et al.* How well do patients with a first episode of schizophrenia respond to antipsychotics: a systematic review and meta-analysis. *Eur Neuropsychopharmacol*. 2017;**27**(9):835–844.
208. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*. 1976;**2**(7992):924–926.
209. Hill D. Cerebral atrophy and cognitive impairment in chronic schizophrenia. *Lancet*. 1976;**2**(7995):1132
210. Baare WF, van Oel CJ, Hulshoff Pol HE, *et al.* Volumes of brain structures in twins discordant for schizophrenia. *Arch Gen Psychiatry*. 2001;**58**(1): 33–40.
211. Veijola J, Guo JY, Moilanen JS, *et al.* Longitudinal changes in total brain volume in schizophrenia: relation to symptom severity, cognition and antipsychotic medication. *PLoS One*. 2014;**9**(7):e101689
212. van Haren NE, Schnack HG, Cahn W, *et al.* Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry*. 2011;**68** (9):871–880.
213. Kubota M, van Haren NE, Haijma SV, *et al.* Association of IQ changes and progressive brain changes in patients with schizophrenia. *JAMA Psychiatry*. 2015;**72**(8):803–812.
214. Boonstra G, van Haren NE, Schnack HG, *et al.* Brain volume changes after withdrawal of atypical antipsychotics in patients with first-episode schizophrenia. *J Clin Psychopharmacol*. 2011;**31**(2):146–153.
215. Lieberman J, Chakos M, Wu H, *et al.* Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry*. 2001;**49**(6): 487–499.
216. Toulopoulou T, Grech A, Morris RG, *et al.* The relationship between volumetric brain changes and cognitive function: a family study on schizophrenia. *Biol Psychiatry*. 2004;**56**(6):447–453.
217. Koutsouleris N, Borgwardt S, Meisenzahl EM, Bottlender R, Moller HJ, Riecher-Rossler A. Disease prediction in the at-risk mental state for psychosis using neuroanatomical biomarkers: results from the FePsy study. *Schizophr Bull*. 2012;**38**(6):1234–1246.
218. Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S, *et al.* Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. *JAMA Psychiatry*. 2018;**75**(11):1156–1172.
219. Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull*. 2013;**39**(5):1129–1138.
220. Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psychiatry*. 1999;**45**(1):17–25.
221. Arnold SE, Trojanowski JQ, Gur RE, Blackwell P, Han LY, Choi C. Absence of neurodegeneration and neural injury in the cerebral cortex in a sample of elderly patients with schizophrenia. *Arch Gen Psychiatry*. 1998;**55**(3):225–232.
222. Bogerts B, Meertz E, Schonfeldt-Bausch R. Basal ganglia and limbic system pathology in schizophrenia. A morphometric study of brain volume and shrinkage. *Arch Gen Psychiatry*. 1985;**42**(8):784–791.
223. Bogerts B, Falkai P, Haupts M, *et al.* Post-mortem volume measurements of limbic system and basal ganglia structures in chronic schizophrenics. Initial results from a new brain collection. *Schizophr Res*. 1990;**3**(5–6): 295–301.
224. Chana G, Landau S, Beasley C, Everall IP, Cotter D. Two-dimensional assessment of cytoarchitecture in the anterior cingulate cortex in major depressive disorder, bipolar disorder, and schizophrenia: evidence for decreased neuronal somal size and increased neuronal density. *Biol Psychiatry*. 2003;**53**(12):1086–1098.
225. Hof PR, Haroutunian V, Friedrich VL Jr., *et al.* Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. *Biol Psychiatry*. 2003;**53**(12):1075–1085.
226. Pakkenberg B. Total nerve cell number in neocortex in chronic schizophrenics and controls estimated using optical disectors. *Biol Psychiatry*. 1993;**34**(11):768–772.
227. Selemon LD, Rajkowska G, Goldman-Rakic PS. Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. *Arch Gen Psychiatry*. 1995;**52** (10):805–818; discussion 819–820.
228. Selemon LD, Kleinman JE, Herman MM, Goldman-Rakic PS. Smaller frontal gray matter volume in postmortem schizophrenic brains. *Am J Psychiatry*. 2002;**159**(12):1983–1991.
229. Stark AK, Uylings HB, Sanz-Arigita E, Pakkenberg B. Glial cell loss in the anterior cingulate cortex, a subregion of the prefrontal cortex, in subjects with schizophrenia. *Am J Psychiatry*. 2004;**161**(5):882–888.
230. Thune JJ, Uylings HB, Pakkenberg B. No deficit in total number of neurons in the prefrontal cortex in schizophrenics. *J Psychiatr Res*. 2001;**35**(1):15–21.
231. McIntosh AM, Owens DC, Moorhead WJ, *et al.* Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis. *Biol Psychiatry*. 2011;**69**(10):953–958.
232. Radua J, Borgwardt S, Crescini A, *et al.* Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. *Neurosci Biobehav Rev*. 2012;**36** (10):2325–2333.
233. van Haren NE, Hulshoff Pol HE, Schnack HG, *et al.* Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. *Neuropsychopharmacology*. 2007;**32**(10):2057–2066.
234. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry*. 2011;**68**(2):128–137.

235. Ho BC, Andreasen NC, Dawson JD, Wassink TH. Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. *Am J Psychiatry*. 2007;**164**(12):1890–1899.
236. Ahmed M, Cannon DM, Scanlon C, *et al.* Progressive brain atrophy and cortical thinning in schizophrenia after commencing clozapine treatment. *Neuropsychopharmacology*. 2015;**40**(10):2409–2417.
237. Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry*. 2012;**2**:e190
238. Van Haren NE, Cahn W, Hulshoff Pol HE, Kahn RS. Confounders of excessive brain volume loss in schizophrenia. *Neurosci Biobehav Rev*. 2013;**37**(10 Pt 1):2418–2423.
239. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry*. 2003;**60**(6):585–594.
240. Vita A, De Peri L, Deste G, Barlati S, Sacchetti E. The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: does the class matter? A meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. *Biol Psychiatry*. 2015;**78**(6):403–412.
241. Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. *Schizophr Bull*. 2013;**39**(6):1363–1372.
242. Murray RM. Mistakes i have made in my research career. *Schizophr Bull*. 2017;**43**(2):253–256.
243. Dorph-Petersen KA, Pierri JN, Perel JM, Sun Z, Sampson AR, Lewis DA. The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology*. 2005;**30**(9):1649–1661.
244. Konopaske GT, Dorph-Petersen KA, Pierri JN, Wu Q, Sampson AR, Lewis DA. Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys. *Neuropsychopharmacology*. 2007;**32**(6):1216–1223.
245. Vernon AC, Natesan S, Modo M, Kapur S. Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. *Biol Psychiatry*. 2011;**69**(10):936–944.
246. Dean CE. Antipsychotic-associated neuronal changes in the brain: toxic, therapeutic, or irrelevant to the long-term outcome of schizophrenia? *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;**30**(2):174–189.
247. Harrison PJ. The neuropathological effects of antipsychotic drugs. *Schizophr Res*. 1999;**40**(2):87–99.
248. Schmitt A, Steyskal C, Bernstein HG, *et al.* Stereologic investigation of the posterior part of the hippocampus in schizophrenia. *Acta Neuropathol*. 2009;**117**(4):395–407.
249. Falkai P, Malchow B, Wetzestein K, *et al.* Decreased oligodendrocyte and neuron number in anterior hippocampal areas and the entire hippocampus in schizophrenia: a stereological postmortem study. *Schizophr Bull*. 2016;**42**(suppl 1):S4–S12.
250. van Kesteren CF, Gremmels H, de Witte LD, *et al.* Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. *Transl Psychiatry*. 2017;**7**(3):e1075.
251. Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain*. 1999;**122**(Pt 4):593–624.
252. Bree AJ, Puente EC, Daphna-Iken D, Fisher SJ. Diabetes increases brain damage caused by severe hypoglycemia. *Am J Physiol Endocrinol Metab*. 2009;**297**(1):E194–E201.
253. Auer RN. Hypoglycemic brain damage. *Metab Brain Dis*. 2004;**19**(3–4):169–175.
254. Rhee SY. Hypoglycemia and dementia. *Endocrinol Metab*. 2017;**32**(2):195–199.
255. Puente EC, Silverstein J, Bree AJ, *et al.* Recurrent moderate hypoglycemia ameliorates brain damage and cognitive dysfunction induced by severe hypoglycemia. *Diabetes*. 2010;**59**(4):1055–1062.
256. Garver DL, Holcomb JA, Christensen JD. Cerebral cortical gray expansion associated with two second-generation antipsychotics. *Biol Psychiatry*. 2005;**58**(1):62–66.
257. Lieberman JA, Tollefson GD, Charles C, *et al.* Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry*. 2005;**62**(4):361–370.
258. Crespo-Facorro B, Roiz-Santianez R, Perez-Iglesias R, *et al.* Effect of antipsychotic drugs on brain morphometry. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;**32**(8):1936–1943.
259. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev*. 2013;**37**(8):1680–1691.
260. Navari S, Dazzan P. Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychol Med*. 2009;**39**(11):1763–1777.
261. Smieskova R, Fusar-Poli P, Allen P, *et al.* The effects of antipsychotics on the brain: what have we learnt from structural imaging of schizophrenia?A systematic review. *Curr Pharm Des*. 2009;**15**(22):2535–2549.
262. Torres US, Portela-Oliveira E, Borgwardt S, Busatto GF. Structural brain changes associated with antipsychotic treatment in schizophrenia as revealed by voxel-based morphometric MRI: an activation likelihood estimation meta-analysis. *BMC Psychiatry*. 2013;**13**(1):342
263. Cahn W, Hulshoff Pol HE, Lems EB, *et al.* Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry*. 2002;**59**(11):1002–1010.
264. Emsley R, Asmal L, du Plessis S, Chiliza B, Phahladira L, Kilian S. Brain volume changes over the first year of treatment in schizophrenia: relationships to antipsychotic treatment. *Psychol Med*. 2017;**47**(12):2187–2196.
265. Lesh TA, Tanase C, Geib BR, *et al.* A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. *JAMA Psychiatry*. 2015;**72**(3):226–234.
266. Rosenberg WM, Deeks J, Lusher A, Snowball R, Dooley G, Sackett D. Improving searching skills and evidence retrieval. *J R Coll Physicians Lond*. 1998;**32**(6):557–563.
267. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club*. 1995;**123**(3):A12–A13.
268. Dawes M, Summerskill W, Glasziou P, *et al.* Sicily statement on evidence-based practice. *BMC Med Educ*. 2005;**5**(1):1
269. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA*. 1992;**268**(17):2420–2425.
270. Rosenberg W, Donald A. Evidence based medicine: an approach to clinical problem-solving. *BMJ*. 1995;**310**(6987):1122–1126.
271. Correll CU, Robinson DG, Schooler NR, *et al.* Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry*. 2014;**71**(12):1350–1363.
272. De Hert M, Detraux J. The urgent need for optimal monitoring of metabolic adverse effects in children and youngsters who take on-label or off-label antipsychotic medication. *JAMA Psychiatry*. 2018;**75**(8):771–772.
273. Lee EHM, Hui CLM, Law EYL, *et al.* Metabolic screening for patients with second-generation antipsychotic medication: a population-based study from 2004 to 2016. *Schizophr Res*. 2018;**197**:618–619.
274. Kasper S, Lowry AJ, Hodge A, Bitter I, Dossenbach M. Tardive dyskinesia: analysis of outpatients with schizophrenia from Africa and the Middle East, Asia, Central and Eastern Europe, and Latin America. *Schizophr Res*. 2006;**81**(2–3):139–143.
275. Takeuchi H, Suzuki T, Uchida H, Watanabe K, Mimura M. Antipsychotic treatment for schizophrenia in the maintenance phase: a systematic review of the guidelines and algorithms. *Schizophr Res*. 2012;**134**(2–3):219–225.
276. Alvarez-Jimenez M, O'Donoghue B, Thompson A, *et al.* Beyond clinical remission in first episode psychosis: thoughts on antipsychotic maintenance vs. guided discontinuation in the functional recovery era. *CNS Drugs*. 2016;**30**(5):357–368.
277. McGorry P, Alvarez-Jimenez M, Killackey E. Antipsychotic medication during the critical period following remission from first-episode psychosis: less is more. *JAMA Psychiatry*. 2013;**70**(9):898–900.
278. Emsley R. On discontinuing treatment in schizophrenia: a clinical conundrum. *NPJ Schizophr*. 2017;**3**:4

279. McNeil TF, Kaij L. Obstetric complications and physical size of offspring of schizophrenic, schizophrenic-like, and control mothers. *Br J Psychiatry*. 1973;**123**(574):341–348.
280. Lewis SW, Mezey GC. Clinical correlates of septum pellucidum cavities: an unusual association with psychosis. *Psychol Med*. 1985;**15**(1):43–54.
281. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *Br Med J (Clin Res Ed)*. 1987;**295**(6600):681–682.
282. Jones P. Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*. 1994;**344**(8934):1398–1402.
283. O'Callaghan E, Sham P, Takei N, Glover G, Murray RM. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet*. 1991;**337** (8752):1248–1250.
284. Wright P, Laing P, Donaldson PT, Murray RM. Schizophrenia: the teratogenic antibody hypothesis. In: Müller N, ed. *Psychiatry, Psychoimmunology, and Viruses*. Vienna, Austria: Springer; 1999:89–99.
285. Murray RM, O'Callaghan E, Castle DJ, Lewis SW. A neurodevelopmental approach to the classification of schizophrenia. *Schizophr Bull*. 1992;**18** (2):319–332.
286. Jones P, Murray RM. The genetics of schizophrenia is the genetics of neurodevelopment. *Br J Psychiatry*. 1991;**158**:615–623.
287. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet*. 2014;**383**(9929):1677–1687.
288. Birley JL, Brown GW. Crises and life changes preceding the onset or relapse of acute schizophrenia: clinical aspects. *Br J Psychiatry*. 1970;**116** (532):327–333.
289. Howes OD, McCutcheon R, Owen MJ, Murray RM. The role of genes, stress, and dopamine in the development of schizophrenia. *Biol Psychiatry*. 2017;**81**(1):9–20.
290. Shorter E. *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac*. John Wiley & Sons; 1997.

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