Continuous maintenance antipsychotic treatment in schizophrenia

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Summary: *During recent years concerns have been raised about the long-term cumulative and potentially negative impact of continuous maintenance antipsychotic treatment of schizophrenia on the human body, especially on the central nervous system.*
This paper aims at providing a summary of literature data on continuous maintenance treatment for practicing physicians.
The results show that continuous maintenance antipsychotic treatment can significantly decrease the risk of relapses and improve the long-term outcome in schizophrenia. Regarding the long-term effects of antipsychotic treatment on the central nervous system, however, further research is needed to answer the question: are brain morphological and functional changes associated with the disease or the treatment or both? 'Based on the data available, low antipsychotic doses are effective and safe while high doses of antipsychotics should be avoided.
This review concludes that the minimum effective doses of antipsychotics should be administered for continuous maintenance treatment.
Keywords: *schizophrenia; antipsychotics; maintenance treatment; mortality; brain volume; therapeutic dose*

Összefoglalás: *Az elmúlt években a szkizofrénia folyamatos fenntartó kezelésében alkalmazott antipszichotikumok emberi szervezetre, különösen az idegrendszerre kifejtett hosszú távú, kumulatív és potenciálisan káros hatása tekintetében több kétely is megfogalmazódott.*
Közleményünk célkitűzése az, hogy a gyakorló klinikusok számára összefoglaljuk a folyamatos fenntartó kezeléssel kapcsolatos irodalmi adatokat.
Az eredmények azt támasztják alá, hogy folyamatos fenntartó antipszichotikus kezeléssel szignifikánsan csökkenthető szkizofréniában a relapszusok rizikója és javítható a betegség hosszú távú kimenetele. Az idegrendszerre kifejtett hosszú távú hatást tekintve még számos kérdés tisztázatlan, és nem egyértelmű, hogy a különféle változások közül mi társul a betegség lefolyásával vagy az antipszichotikus kezelés hatékonyságával és mellékhatásaival. A rendelkezésre álló adatok szerint meghatározható az antipszichotikumok hatékony és biztonságos adagja, és kerülni kell a magas antipszichotikus dózisok alkalmazását.
Áttekintő közleményünk konklúziója, hogy a folyamatos fenntartó kezelés során a minimálisan hatékony antipszichotikum adagok alkalmazására kell törekedni.
Kulcsszavak: *szkizofrénia, antipszichotikumok, fenntartó kezelés, mortalitás, agyvolumen, terápiás dózis*

1. Introduction

A generally accepted consensus based on guidelines on the treatment of schizophrenia (e.g. [1–3]) is that treatment with antipsychotics plays a key role in preventing relapses, which are associated with poor outcomes. However, a number of papers have been published during recent years that expressed doubts about the usefulness of continuous maintenance treatment in schizophrenia (4–6). These papers raised important issues, such as the long-term, cumulative and potentially harmful effect of antipsychotics on the central nervous system, in respect of which only limited scientific data are available; in addition, they also expressed concerns about somatic adverse effects and mortality data. These papers raise relevant

questions about the benefits and disadvantages of antipsychotics, and encourage experts to review the currently available data on the treatment of schizophrenia (7–9). A meta-analysis of the data obtained during the last 60 years clearly demonstrates the efficacy of antipsychotics vs. placebo in acute stages of schizophrenia (10) and there is a high degree of consensus on the need to administer antipsychotics in the acute phase of schizophrenia. The differences in the viewpoints are mainly about long-term antipsychotic treatment. The complexity of this question is also shown by the very limited data available on medication discontinuation: what degree of symptomatic improvement is necessary (e.g. remission associated with low severity of the symptoms, or full remission of symptoms), and what is the time period after achieving stabilization/remission/recovery when medication may be discontinued (1, 11, 12)?

This review attempts to provide an accurate account of the current concerns and debates about long-term antipsychotic maintenance treatment; the relevant references are listed accordingly. We also tried to select the references to use the best available evidence-based research data, therefore, if there was any meta-analysis or systematic review about a topic, we used it. Our goal was not to compile a systematic review of a specific period, but rather to provide practicing physicians with a comprehensive review that supports the planning of long-term maintenance antipsychotic treatment.

2. The importance of relapses

The main objectives of long-term maintenance treatment are symptom control and relapse prevention. However, the question arises about the importance of relapses for the long-term outcome, including the question about their potential „neurotoxic" effects. Though the majority of the data provide a quite clear picture about the negative consequences of relapses (9, 12), it should be noted that the data on the effect of relapses causing progression are mostly of an indirect nature (12). A significant proportion of patients respond well to treatment in the early phases of the disease, however this is not the case in later stages of schizophrenia, after several relapses (13). The data also indicate that lower doses of antipsychotics would be sufficient, especially in the early stages (14). The high relapse rates draw attention to the importance of relapse prevention: according to a systematic review by *Zipursky et al.* (15), after the first episode of schizophrenia 77% and 90% of patients experienced relapse within one year and two years, respectively, after discontinuing antipsychotic treatment, while the relapse rate was only 3% if maintenance treatment was administered. According to a long-term study, persistent symptomatic and functional remission after the first episode determines the likelihood of recovery (16). Furthermore, recurring relapses are associated with an increasing proportion of treatment-resistant patients (17, 18) and more and more time is needed to achieve treatment response and remission (19). A 5-year longitudinal study showed that the incidence of relapse-related psychotic states is associated with an extensive reduction of gray matter volume, which indicates that relapses have „neurotoxic" effects (20). However, it is not entirely clear whether the negative effects of relapses are generally characteristic for the disease course or are limited to a subset of patients with poor prognosis who have residual symptoms after relapses (17, 18). The latter seems to be contradicted by the fact that response to antipsychotic treatment is significantly impaired after a relapse even in patients who have an excellent response to and achieve symptomatic and functional remission after the first treatment (21). In addition, based on his own results, *Emsley et al.* (17) suggest that reduced response can be prevented by resuming the antipsychotic treatment in due time, during the early phase of relapse after discontinuing the medication. This hypothesis is consistent with the view that the disease course could be negatively impacted not only by the number but also by the duration of the relapses (12, 22). The latter has been supported by a meta-analy-

sis on the effects of the duration of untreated psychosis (23), which showed that the longer the disease remained untreated, the worse the symptomatic and functional outcome will be.

In sum: Long-term studies show that the number and duration of relapses and the duration of untreated psychosis result in worse disease course and outcome.

3. Is continuous maintenance antipsychotic treatment necessary?

The question whether continued administration of prophylactic antipsychotics or treatment discontinuation after stabilization is associated with better outcomes could be explored by long-term placebo-controlled studies (8). There are currently no studies available that did not use antipsychotics in the acute phase either. There are ethical reasons for this, since failure to administer treatment may be associated with a potentially significant progression of the disease (24, 25). In addition, the data show that placebo-controlled studies are usually discontinued early, mainly due to the high relapse rate (24). These data also confirm the need for maintenance treatment but there are some naturalistic studies that may give an indication of how the administration or the lack of maintenance antipsychotic treatment can influence the long-term outcome of the disease. A Chinese naturalistic study that followed patients for 14 years showed that treatment-naïve patients had a worse outcome: the rates of partial or complete remissions were lower in these patients compared to those who received maintenance treatment (29.8% and 53.7%, respectively), with higher rates of homelessness and mortality (26).

Nevertheless, there are a number of systematic reviews and meta-analyses available to help decision-making about maintenance treatment, providing a comprehensive view on the topic. These types of analyses usually compare three treatment models: continuous maintenance treatment; intermittent treatment (controlled discontinuation and restart of treatment as planned or when symptoms reoccur); and treatment with a placebo. According to a Cochrane analysis, intermittent treatment is not as effective in preventing relapse and hospitalization as continuous maintenance treatment, yet it is still more effective than placebo (27). Another study came to similar conclusions (7). Maintenance treatment with first-generation and second-generation antipsychotics significantly reduced the number of relapses in patients both after the first episode and after several episodes. With intermittent treatment and placebo the risk of relapse increased three-fold and six-fold, respectively, as compared to continuous treatment (7). Patients who received continuous treatment had no relapse for a significantly longer period of time: the mean time to relapse was 11–14 months for intermittent treatment and 5 months for placebo (7). A systematic review of studies related to the first psychotic episode (28) showed that the application of maintenance treatment after a psychotic episode is more effective than discontinuation of treatment or intermittent treatment. Maintenance treatment resulted in a higher likelihood of remission, while lack of this treatment reduced the chance of later achieving remission (28). Moreover, maintenance treatment was associated with better cognitive functions. Maintenance treatment is further supported by a meta-analysis by *Leucht et al.* (11), which showed that this treatment significantly reduced the rate of relapse after one year (maintenance treatment: 27%; discontinuation: 64%). A more recent analysis (29) also demonstrated that maintenance treatment prevented significant deterioration for a year, and discontinuation of treatment led almost immediately to the deterioration of the symptoms. This deterioration showed a linear correlation with the number of relapses. In a paper published in spring 2017, *Goff et al.* (8) reviewed the long-term effects of maintenance antipsychotic treatment. This paper concluded that both antipsychotic treatment administered in the early stages of schizophrenia and maintenance treatment are well-documented evidence-based treatments and improve long-term outcomes.

This means that all reviews, systematic reviews and meta-analyses reached the same conclusions (7, 8, 11, 27, 29): continuous maintenance antipsychotic treatment has a positive effect on the outcome of schizophrenia. However, it should be noted that many issues are still unclear. For example, it seems that there is a subset of patients who did not experience relapse despite taking placebo. There is only limited information on the characteristics of this population and on how long this status can be maintained. The generalizability of the results of placebo-controlled studies is limited by many factors, including the data showing that active treatment is usually discontinued faster than recommended by most recent guidelines (e.g. Australian and New Zealand Guidelines recommend 3 to 6 months [1]), which can result in a psychotic state associated with relapse, rebound or withdrawal symptoms.

In sum: Evidence-based data show that continuous maintenance antipsychotic treatment is more effective in preventing relapse and ensures a longer relapse-free period compared to intermittent and placebo treatments. Thus, the superiority of continuous antipsychotic treatment is confirmed by meta-analyses, but there are no meta-analyses or systematic reviews showing that intermittent or placebo treatments (or no treatment) are equally or more effective than continuous antipsychotic treatment.

4. The issue of the antipsychotic dose

Most of the concerns about continuous maintenance treatment of schizophrenia (4–6) assume that long-term administration of antipsychotics may contribute to the reduction of the brain volume (22, 30, 31) and might have a negative effect on cognitive functions (32, 33), which might result in poor disease outcomes. Although the conclusions suggesting causal relationships are not widely shared (8, 34), this is still an issue that presents physicians with a dilemma: lack of treatment can potentially result in a worse outcome due to relapses and the „toxicity" of the psychotic periods, but antipsychotic treatment, especially in high doses, can have negative consequences as well. However, it should be noted that current data fail to answer the question whether effective but low/er doses of antipsychotics contribute to the progressive reduction of the brain volume (8). In addition, it should be taken into account (8) that there can be significant differences between various antipsychotics since, for example, there are data showing that contrary to first-generation agents, second-generation antipsychotics do not have or may have only a limited „neurotoxic effect" (35).

In the light of these inconsistent data, one should attempt to adopt a rational therapeutic approach. Randomized studies strongly support the positive effects of antipsychotics in the recommended „safe" dose ranges. However, there is a paucity of data indicating which dose ranges can be considered to be safe. Long-term follow-up studies have shown that the intensity of the antipsychotic treatment can influence the reduction of the brain volume (22, 36), and longitudinal meta-analyses suggest that the higher the average daily dose or the total antipsychotic exposure, the more pronounced is the reduction of the brain volume (30, 35, 37). These data support that antipsychotic doses should be kept minimal but still in the effective range, and high and especially megadoses should be avoided. A recent study (38) monitoring the changes in brain volume in patients after the first psychotic episode for one year, provides some guidance on dosing. The chlorpromazine equivalent dose was 241 mg at baseline and 313 mg at the one-year follow-up assessment. Though the study found a relationship between dose and the reduction of brain volume, there was no significant reduction compared to healthy controls. The relationships between antipsychotics and brain volume should be treated with caution because a systematic analysis of studies on the effects of antipsychotics on brain volume showed that these correlations were not always significant in the original studies, and were often found on a small sample

using extremely heterogeneous methods and potentially modifying factors were frequently not considered (39). However, it is important to note that the impact of the inclusion of patients who presumably received high doses of first-generation antipsychotics (according to treatment principles significantly different from today's in the early era of antipsychotics, or before the introduction of second-generation antipsychotics) is not clear. Many of these patients still continue to receive high-dose treatment (40). For example, the incidence of tardive dyskinesia (TD) is dramatically lower in patients who have never received first-generation antipsychotics (41).

It should also be noted that the relationships between the treatment, the severity of symptoms and the effects on the central nervous system are quite unclear. A paper by *Lesh et al.* (42) describes that patients with first-episode schizophrenia taking antipsychotics had a more pronounced reduction in thickness of the cortex, as compared to untreated patients with first-episode schizophrenia; however, the treated group had better cognitive performance and their brain activity patterns were more similar to those in healthy people than in untreated patients with schizophrenia.

Moreover, making a distinction between the effects resulting from the pathophysiology of the disease and from the antipsychotics continues to be challenging (38). In this respect, account must also be taken of the fact that when more severe and/or persistent symptoms occur, showing no or little improvement during treatment, physicians usually increase the antipsychotic dose. Thus, brain changes caused by the disease and/or by the medication cannot be easily separated on the basis of data obtained in studies not comparing fixed doses.

In sum: Taken together, the harmful consequences of the failure to administer antipsychotic treatment and the potentially negative effects of long-term antipsychotic treatment in schizophrenia, the wisest action would be to administer the lowest effective dose of an antipsychotic.

5. Antipsychotic treatment and tardive dyskinesia (TD)

Long-term antipsychotic treatment is associated with an increase in the incidence of some adverse effects. One of the most severe adverse effects of long-term antipsychotic treatment is TD. Some hypotheses assume that TD is a sign of the sensitization of the dopamine system (43), which may also play a role in the development of treatment-resistance and supersensitive psychosis (6, 44, 45). According to these hypotheses, long-term postsynaptic blockade leads to upregulation of D2 receptors, which can play a role in the development of tolerance to antipsychotics and treatment-resistance (46), and in „supersensitive psychosis", which occurs shortly after the reduction of the medication concentration. Some studies found that TD, tolerance to antipsychotics and supersensitive psychosis are more commonly associated with treatment-resistant patients (45). Nonetheless, these data suggest that these phenomena are more likely to occur in a subgroup of treatment-resistant patients with deficit symptoms. The role of the long-term treatment is also unclear because a meta-analysis showed that TD has similar incidence with continuous and intermittent treatments (27). The data also suggest that the more frequently interrupted the treatment, the higher the risk of TD (47). TD is still frequent; a recent meta-analysis reported a prevalence rate of 25.3% (41). However, the prevalence is very different for first-generation and second-generation antipsychotics. TD is more frequent in patients receiving first-generation antipsychotics vs. second-generation antipsychotics: 30% and 20.7% respectively (41). Based on the data available, it is difficult to evaluate the extent to which former exposure to first-generation antipsychotics influences the TD prevalence of 20.7% in patients recently treated with second-generation antipsychotics. In any case, TD prevalence is significantly lower (7.2%) in patients who received exclusively second-generation antipsychotic treatment. The use of second-generation agents may reduce the TD risk associated with first-generation

agents (41). This is supported by the findings that prevalence is lower in the case of a combination of first-generation and second-generation antipsychotics (22.7%) than in the case of a first-generation monotherapy (30%) (41).

Thus, these relationships are far from being clear. Though there are animal model data evaluating the role of antipsychotics in the sensitization of the striatal dopamine system (46, 48), the results cannot be easily extrapolated to human subjects (49). The dopamine hypothesis of schizophrenia assumes presynaptic dopamine hyperactivity and data also indicate an increase in the number of postsynaptic D2/3 receptors (50, 51).

Dosing of antipsychotics can play an important role in D2 receptor upregulation. According to some data from animal studies, the increase in the number of receptors was associated with high-dose antipsychotic treatments that result in D2 receptor blockade above 80%, which frequently causes extrapyramidal side effects in humans (52). However, TD and supersensitive psychosis may not be caused by the same mechanisms – TD is mostly irreversible, while supersensitive psychosis is not (53). A further issue is that supersensitive psychosis, which is considered to be associated with rapid dissociation of the antipsychotics from the dopamine receptors (54) and some other pharmacodynamic or pharmacokinetic factors (12), cannot be clinically distinguished from rebound psychosis.

In sum: It is not clearly demonstrated that the dopamine system is hypersensitized as a result of long-term antipsychotic treatment, and it cannot be stated with certainty that TD, tolerance to antipsychotics or supersensitive psychosis are caused by the same pathological mechanisms. The results from TD research suggest that second-generation antipsychotics are considerably safer.

6. Antipsychotic treatment and mortality

During recent years, in addition to TD, metabolic adverse effects received a great deal of attention because second-generation antipsychotics are frequently associated with metabolic abnormalities, which can contribute to higher mortality in schizophrenia (55). However, the evaluation of metabolic disorders in schizophrenia is difficult since they are also more common in patients who did not receive antipsychotics (56, 57). It has been suggested that schizophrenia and diabetes mellitus share a common genetic basis (58). Longitudinal data from the last decades show an increasing gap in mortality rates between patients with schizophrenia and the general population (59). While average life expectancy increased worldwide, this tendency cannot be observed in patients with schizophrenia (60). In addition to suicides, unhealthy lifestyle (such as smoking, lack of exercise and nutritional problems), poverty, inadequate medical care and more frequent accidents also play a role in the higher mortality rates, and correlation with treatment-related side effects and somatic comorbidities was also found (60–64). Most recently, a Hungarian cohort study showed that schizophrenia was associated with a 2.4-fold increase in the relative risk of mortality (64), which was significantly related to somatic comorbidities in addition to suicide death. The higher mortality associated with schizophrenia is caused mainly by cardiovascular diseases (60). In this respect, antipsychotics may also play a role, especially due to the metabolic adverse effects (55), but studies also concluded that long-term antipsychotic treatment reduced the risk of mortality (65, 66) compared to patients who did not receive medication. The high mortality rate in the latter group can be explained not only by psychiatric events (such as suicide or violence), but mainly by the fact that they do not use health resources and are less preoccupied with their general health (e.g. high rates of smoking, lack of exercise and nutritional problems) (66, 67). However, *Osborn et al.* (68) reported that high-dose antipsychotic

treatment is associated with increased risk of cardiovascular death. Furthermore, longitudinal studies and meta-analyses suggest that this correlation is complex: high risk of deaths was associated with both high doses of antipsychotics and lack of antipsychotic treatment, while this risk was the lowest in patients treated with low/medium doses of antipsychotics (66, 69).

In sum: These results also draw attention to the need to administer the lowest effective dose, as the mortality risk is lowest in patients treated with low/medium doses of antipsychotics (66, 69).

7. Planning and monitoring antipsychotic treatment

Systematic reviews and meta-analyses show that continuous maintenance treatment results in a better course and outcome of schizophrenia, but further data are needed to properly address the concerns about the potential negative effects of such treatment.

Both the results of imaging studies and the mortality data provide support for the administration of an effective but low dose. In this respect, however, the various guidelines are far from being clear, with some recommending maintaining the dose that was effective in the acute phase (e.g.[1]), while others suggest the administration of the lowest but still effective dose (e.g. [70]). Low-dose treatment has also been increasingly included in the therapeutic guidelines, which now recommend a lower dose than in the past (71), and the administration of megadoses, related to rapid neuroleptization (72, 73) is no longer recommended (74). In a prospective, randomized double-blind study, patients randomized to low haloperidol plasma levels showed similar improvement compared to patients randomized to medium or high levels (75). Though there is only limited data available on antipsychotic doses used in practice, it seems that even if no megadoses were used, the administration of high doses is frequent, e.g. 38% to 64.4% of hospitalized patients received high-dose treatment (76, 77), and this rate was significant in the age group over 50 (40). Some data show that though the rate of high-dose antipsychotic treatments administered as monotherapy decreased, high-dose antipsychotic combination therapies became more common (77–79).

Analyses of different doses showed that maintenance treatment with low doses is as effective as with standard doses. *Uchida et al.* (80) defined standard dose as the defined daily dose (DDD) published by the World Health Organization (WHO) (daily maintenance dose determined for an adult patient with moderate disease, https://www.whocc.no/ atc_ddd_ index/?code=N05A) (Table 1), and established that the low dose (50–100% of DDD) was as effective as the standard dose in relapse and hospitalization prevention. However, a very low dose (less than 50% of DDD) was not effective. A low dose calculated on the basis of DDD showed a strong similarity with the minimal effective doses used to calculate dose equivalency introduced by *Leucht et al.* (81). These values constitute a good point of reference in determining the lowest effective dose of a

Table 1.
Daily Defined Dose (DDD)

	Oral dose	Depot dose
aripiprazole	15 mg	13.3 mg
amisulpride	400 mg	
asenapine	20 mg	
clozapine	300 mg	
chlorpromazine	300 mg	
chlorprothixene	300 mg	
flupentixol	6 mg	4 mg
fluphenazine	10 mg	1 mg
haloperidol	8 mg	3.3 mg
lurasidone	60 mg	
olanzapine	10 mg	10 mg
paliperidone	6 mg	2.5 mg
quetiapine	400 mg	
risperidone	5 mg	2.7 mg
sertindole	16 mg	
sulpiride	800 mg	
tiapride	400 mg	
ziprasidone	80 mg	
zuclopenthixol	30 mg	15 mg

https://www.whocc.no/atc_ddd_index/?code=N05A

specific antipsychotic. The best way to avoid the potentially negative effects of long-term treatment seems to be to determine the minimal effective dose by small dose adjustments. If required, temporary benzodiazepine augmentation may also be used to control symptoms, until full antipsychotic effect is achieved, instead of rapidly increasing the antipsychotic dose (1, 82, 83).

The development of extrapyramidal symptoms shows that the rate of receptor blockade exceeded the limit for adverse effects (84); moreover, early extrapyramidal symptoms (EPS) is a strong predictor of TD (85). A „reverse" neuroleptic approach, developed in the 1950s, is true: „neuroleptic" effects (extrapyramidal symptoms) reflect not the therapeutic effect, but side effects and a potentially dangerous antipsychotic dose. Therefore, it is important to monitor the adverse effects. In addition to the known scales used to measure extrapyramidal symptoms (such as the Simpson-Angus Scale or Barnes Akathisia Scale), early EPS symptoms can be easily detected using a handwriting test in clinical practice (53, 86). It is also important to monitor other side effects, including the metabolic parameters (body weight, body mass index, blood glucose, triglycerides and HDL cholesterol) (87). The vulnerability to adverse effects is especially high in young people (early stages of the disease), when a more careful strategy is recommended.

When selecting antipsychotics, the data showing differences in the efficacy and safety profiles of second-generation antipsychotics should be taken into account (88, 89). The benefits of second-generation antipsychotics are emphasized by the favorable results related to the lower reduction of the brain volume (20, 35) and the lower incidence of TD as compared to first-generation antipsychotics (41). Interactions and pharmacokinetic properties should also be considered (90).

Monitoring the treatment (therapeutic and side effects) is of decisive importance. The evaluation of adherence should start in the early phases of the treatment (91), and the use of long-acting injections should also be already considered in the early phases, since their use reduces the risk of relapses and rehospitalization compared to equivalent oral agents (92, 93). In addition, the dose exposure is usually lower due to more favorable pharmacokinetic parameters (94).

8. Limitations

This paper focuses on issues, hypotheses and concerns related to continuous maintenance treatment of schizophrenia, especially on those based on the dopamine hypothesis of schizophrenia. As a consequence, we did not discuss to what extent these concerns can be interpreted within the framework of the dopamine hypothesis (See: [95, 96]). Furthermore, this paper did not address the relationship between the first psychotic episode and schizophrenia, and it addressed specific treatment aspects of the first psychotic episode only in part. While it is generally accepted in the literature that 10% to 20% of patients with schizophrenia suffer only one episode, currently there are no reliable diagnostics guidelines to separate this population from those who suffer several relapses without appropriate antipsychotic treatment (7, 97). Treatment-resistance was beyond the scope of this paper as well, since it cannot be interpreted only in terms of the dopamine hypothesis (98). This paper does not provide a comprehensive overview about safe and effective antipsychotic doses. Furthermore, we did not discuss the different definitions of equivalent doses, which can be used to compare antipsychotics (81, 99, 100).

9. Conclusions

Despite all doubts, current evidence shows that continuous maintenance antipsychotic treatment helps to prevent relapses and to improve long-term outcomes (8). The efficacy of maintenance antipsychotic treatment is one of the best-documented results in psychiatry, and its efficacy is comparable to well-established

treatments for internal and other diseases (8, 101). Several questions still remain unanswered, e.g. about the long-term effects of antipsychotics on the central nervous system, and it is not clear which changes are related to the pathophysiology of the disease and which ones to the therapeutic effects or the side effects of the medicine (42). In any case, the mortality data also show that there is a safe low/medium dose range but the administration of needlessly high doses should be avoided (66). Overall, it is recommended to always administer the minimal effective dose because this allows the maximization of the therapeutic benefit and a significant reduction of potentially harmful effects.

References

1. GALLETLY C, CASTLE D, DARK F, HUMBERSTONE V, JABLENSKY A, KILLACKEY E et al.: Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 2016; 50: 410–472.
2. NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE. Psychosis and schizophrenia in adults: prevention and management. NICE guidelines [CG178], 2014.
3. HASAN A, FALKAI P, WOBROCK T, LIEBERMAN J, GLENTHOJ B, GATTAZ WF et al.: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry 2012; 13: 318–378.
4. MONCRIEFF J: Antipsychotic maintenance treatment: time to rethink? PLoS Med 2015; 12: e1001861–e1001867.
5. GOTZSCHE PC, YOUNG AH, CRACE J: Does long term use of psychiatric drugs cause more harm than good? BMJ 2015; 350: h2435–h2435.
6. MURRAY RM, QUATTRONE D, NATESAN S, VAN OS J, NORDENTOFT M, HOWES O et al.: Should psychiatrists be more cautious about the long-term prophylactic use of antipsychotics? Br J Psychiatry 2016; 209: 361–365.
7. DE HERT M, SERMON J, GEERTS P, VANSTEELANDT K, PEUSKENS J, DETRAUX J: The use of continuous treatment versus placebo or intermittent treatment strategies in stabilized patients with schizophrenia: a systematic review and meta-analysis of randomized controlled trials with first- and second-generation antipsychotics. CNS Drugs 2015; 29: 637–658.
8. GOFF DC, FALKAI P, FLEISCHHACKER WW, GIRGIS RR, KAHN RM, UCHIDA H et al.: The long-term effects of antipsychotic medication on clinical course in schizophrenia. Am J Psychiatry 2017; 174: 840-849.
9. CATTS SV, O'TOOLE BI: The treatment of schizophrenia: can we raise the standard of care? Aust N Z J Psychiatry 2016; 50: 1128–1138.
10. LEUCHT S, LEUCHT C, HUHN M, CHAIMANI A, MAVRIDIS D, HELFER B 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; appiajp201716121358.
11. LEUCHT S, TARDY M, KOMOSSA K, HERES S, KISSLING W, SALANTI G et al.: Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 2012; 379: 2063–2071.
12. EMSLEY R, CHILIZA B, ASMAL L, HARVEY BH: The nature of relapse in schizophrenia. BMC Psychiatry 2013; 13: 50.
13. LIEBERMAN J, JODY D, GEISLER S, ALVIR J, LOEBEL A, SZYMANSKI S et al.: Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry 1993; 50: 369-376.
14. MCGORRY PD, COCKS J, POWER P, BURNETT P, HARRIGAN S, LAMBERT T: Very low-dose risperidone in first-episode psychosis: a safe and effective way to initiate treatment. Schizophr Res Treatment 2011; 2011: 631690.
15. ZIPURSKY RB, MENEZES NM, STREINER DL: Risk of symptom recurrence with medication discontinuation in first-episode psychosis: A systematic review. Schizophr Res 2014; 152: 408–414.
16. ÁLVAREZ-JIMÉNEZ M, GLEESON JF, HENRY LP, HARRIGAN SM, HARRIS MG, KILLACKEY E et al.: Road to full recovery: longitudinal relationship between symptomatic remission and psychosocial recovery in first-episode psychosis over 7.5 years. Psychol Med 2012; 42: 595–606.
17. 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: 80–83.
18. 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: 75–85.
19. LIEBERMAN JA, ALVIR JM, KOREEN A, GEISLER S, CHAKOS M, SHEITMAN B et al.: Psychobiologic correlates of treatment response in schizophrenia. Neuropsychopharmacology 1996; 14 Suppl 3: 13S–21S.
20. VAN HAREN NEM, HULSHOFF POL HE, SCHNACK HG, CAHN W, MANDL RC, COLLINS DL et al.: Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 2007; 32: 2057–2066.
21. MAYORAL-VAN SON J, LA FOZ DE VO-G, MARTINEZ-GARCIA O, MORENO T, PARRILLA-ESCOBAR M, VALDIZAN EM et al.: Clinical outcome after antipsychotic treatment discontinuation in functionally recovered first-episode nonaffective psychosis individuals. J Clin Psychiatry 2016; 77: 492–500.
22. ANDREASEN NC, LIU D, ZIEBELL S, VORA A, HO B-C: Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. Am J Psychiatry 2013; 170: 609–615.
23. 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: 88–94.
24. FLEISCHHACKER WW, CZOBOR P, HUMMER M, KEMMLER G, KOHNEN R, VOLAVKA J: Placebo or active control trials of antipsychotic drugs? Arch Gen Psychiatry 2003; 60: 458–464.
25. STROUP TS, ALVES WM, HAMER RM, LIEBERMAN JA: Clinical trials for antipsychotic drugs: design conventions, dilemmas and innovations. Nat Rev Drug Discov 2006; 5: 133–146.
26. RAN MS, WENG X, CHAN CL, CHEN EY, TANG CP, LIN FR 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: 495–500.
27. SAMPSON S, JOSHI K, MANSOUR M, ADAMS CE: Intermittent drug techniques for schizophrenia. Schizophr Bull 2013; 39: 960–961.
28. KARSON C, DUFFY RA, ERAMO A, NYLANDER A-G, OFFORD S: Long-term outcomes of antipsychotic treatment in patients with first-episode schizophrenia: a systematic review. Neuropsychiatr Dis Treat 2016; 12: 57–67.
29. 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: 137-143.

30. 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: 1680–1691.

31. MOILANEN J, HUHTANISKA S, HAAPEA M, JÄÄSKELÄINEN E, VEIJOLA J, ISOHANNI M et al.: Brain morphometry of individuals with schizophrenia with and without antipsychotic medication – The Northern Finland Birth Cohort 1966 Study. Eur Psychiatry 2015; 30: 598–605.

32. HUSA AP, MOILANEN J, MURRAY GK, MARTTILA R, HAAPEA M, RANNIKKO I et al.: Lifetime antipsychotic medication and cognitive performance in schizophrenia at age 43 years in a general population birth cohort. Psychiatry Res 2017; 247: 130–138.

33. BORA E, MURRAY RM: Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: do the cognitive deficits progress over, or after, the onset of psychosis? Schizophr Bull 2014; 40: 744–755.

34. ROIZ-SANTIÁÑEZ R, SUAREZ-PINILLA P, CRESPO-FACORRO B: Brain structural effects of antipsychotic treatment in schizophrenia: a systematic review. Curr Neuropharmacol 2015; 13: 422–434.

35. 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: 403–412.

36. HO B-C, 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: 128–137.

37. 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.

38. JØRGENSEN KN, NESVÅG R, NERLAND S, MØRCH-JOHNSEN L, WESTLYE LT, LANGE EH et al.: Brain volume change in first-episode psychosis: an effect of antipsychotic medication independent of BMI change. Acta Psychiatr Scand 2017; 135: 117–126.

39. HUHTANISKA S, JÄÄSKELÄINEN E, HIRVONEN N, REMES J, MURRAY GK, VEIJOLA J et al.: Long-term antipsychotic use and brain changes in schizophrenia – a systematic review and meta-analysis. Hum Psychopharmacol Clin Exp. 2017;32:e2574.

40. XIANG Y-T, LI Y, CORRELL CU, UNGVARI GS, CHIU HF, LAI KY et al.: Common use of high doses of antipsychotic medications in older Asian patients with schizophrenia (2001-2009). Int J Geriatr Psychiatry 2014; 29: 359–366.

41. CARBON M, HSIEH C-H, KANE JM, CORRELL CU: Tardive dyskinesia prevalence in the period of second-generation antipsychotic use: a meta-analysis. J Clin Psychiatry 2017; 78: e264–e278.

42. LESH TA, TANASE C, GEIB BR, NIENDAM TA, YOON JH, MINZENBERG MJ et al.: A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. JAMA Psychiatry 2015; 72: 226–234.

43. CHOUINARD G, JONES BD: Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry 1980; 137: 16–21.

44. FALLON P, DURSUN S, DEAKIN B: Drug-induced supersensitivity psychosis revisited: characteristics of relapse in treatment-compliant patients. Ther Adv Psychopharmacol 2012; 2: 13–22.

45. SUZUKI T, KANAHARA N, YAMANAKA H, TAKASE M, KIMURA H, WATANABE H et al.: Dopamine supersensitivity psychosis as a pivotal factor in treatment-resistant schizophrenia. Psychiatry Res 2015; 227: 278–282.

46. ODA Y, KANAHARA N, IYO M: Alterations of dopamine D2 receptors and related receptor-interacting proteins in schizophrenia: the pivotal position of dopamine supersensitivity psychosis in treatment-resistant schizophrenia. Int J Mol Sci 2015; 16: 30144–30163.

47. VAN HARTEN PN, HOEK HW, MATROOS GE, KOETER M, KAHN RS: Intermittent neuroleptic treatment and risk for tardive dyskinesia: Curacao Extrapyramidal Syndromes Study III. Am J Psychiatry 1998; 155: 565–567.

48. TADOKORO S, OKAMURA N, SEKINE Y, KANAHARA N, HASHIMOTO K, IYO M: Chronic treatment with aripiprazole prevents development of dopamine supersensitivity and potentially supersensitivity psychosis. Schizophr Bull 2012; 38: 1012–1020.

49. CATTS SV, O'TOOLE BI: Reducing long-term antipsychotic use: a therapeutic dead end? Br J Psychiatry 2017; 210:368.

50. HOWES OD, KAMBEITZ J, KIM E, STAHL D, SLIFSTEIN M, ABI-DARGHAM A et al.: The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Arch Gen Psychiatry 2012; 69: 776–786.

51. WEINSTEIN JJ, CHOHAN MO, SLIFSTEIN M, KEGELES LS, MOORE H, ABI-DARGHAM A: Pathway-Specific Dopamine Abnormalities in Schizophrenia. Biol Psychiatry 2017; 81: 31–42.

52. 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: 662–671.

53. BITTER I: Antipszichotikumok. In: BITTER I, RIHMER Z: Gyakorlati pszichofarmakológia (Antipsychotics. In: BITTER I, RIHMER Z: Psychopharmacology in Clinical Practice). Medicina, Budapest, 1989, 34–83. (Book Chapter in Hungarian)

54. KAPUR S, SEEMAN P: Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: a new hypothesis. Am J Psychiatry 2001; 158: 360–369.

55. 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: 119–136.

56. PAPANASTASIOU E: The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Ther Adv Psychopharmacol 2013; 3: 33–51.

57. MITCHELL AJ, VANCAMPFORT D, SWEERS K, VAN WINKEL R, YU W, DE HERT M: Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – a systematic review and meta-analysis. Schizophr Bull 2011; 39: 306–318.

58. HANSEN T, INGASON A, DJUROVIC S, MELLE I, FENGER M, GUSTAFSSON O et al.: At-risk variant in TCF7L2 for type II diabetes increases risk of schizophrenia. Biol Psychiatry 2011; 70: 59–63.

59. SAHA S, CHANT D, MCGRATH J: A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 2007; 64: 1123–1131.

60. OLFSON M, GERHARD T, HUANG C, CRYSTAL S, STROUP TS: Premature mortality among adults with schizophrenia in the United States. JAMA Psychiatry 2015; 72: 1172–1181.

61. CRUMP C, WINKLEBY MA, SUNDQUIST K, SUNDQUIST J: Comorbidities and mortality in persons with schizophrenia: a Swedish national cohort study. Am J Psychiatry 2013; 170: 324–333.

62. ROBINSON DG: Early mortality among people with schizophrenia. Am J Psychiatry 2016; 173: 554–555.

63. LEUCHT S, BURKARD T, HENDERSON J, MAJ M, SARTORIUS N: Physical illness and schizophrenia: a review of the literature. Acta Psychiatr Scand 2007; 116: 317–333.

64. BITTER I, CZOBOR P, BORSI A, FEHÉR L, NAGY BZ, BACSKAI M et al.: Mortality and the relationship of somatic comorbidities to mortality in schizophrenia. A nationwide matched-cohort study. Eur Psychiatry 2017; 45: 97–103.

65. TIIHONEN J, LÖNNQVIST J, WAHLBECK K, KLAUKKA T, NISKANEN L, TANSKANEN A et al.: 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet 2009; 374: 620–627.

66. VERMEULEN J, VAN ROOIJEN G, DOEDENS P, NUMMINEN E, VAN TRICHT M, DE HAAN L:
Antipsychotic medication and long-term mortality risk in patients with schizophrenia; a systematic review and meta-analysis. Psychol Med 2017; 47: 2217-2228.

67. COPELAND LA, ZEBER JE, WANG C-P, PARCHMAN ML, LAWRENCE VA, VALENSTEIN M et al.:
Patterns of primary care and mortality among patients with schizophrenia or diabetes: a cluster analysis approach to the retrospective study of healthcare utilization. BMC Health Serv Res 2009; 9: 127.

68. OSBORN D, LEVY G, NAZARETH I, PETERSEN I, ISLAM A, KING MB:
Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. Arch Gen Psychiatry, 2007; 64: 242–249.

69. TORNIAINEN M, MITTENDORFER-RUTZ E, TANSKANEN A, BJÖRKENSTAM C, SUVISAARI J, ALEXANDERSON K et al.:
Antipsychotic treatment and mortality in schizophrenia. Schizophr Bull 2015; 41: 656–663.

70. LEHMAN AF, LIEBERMAN JA, DIXON LB, MCGLASHAN TH, MILLER AL, PERKINS DO:
Practice guidelines for the treatment of patients with schizophrenia, 2nd edition. Am J Psychiatry 2004; 161 (Suppl 2): 1-56.

71. HASAN A, FALKAI P, WOBROCK T, LIEBERMAN J, GLENTHOJ B, GATTAZ WF et al.:
World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry 2013; 14: 2–44.

72. DONLON PT, HOPKIN J, TUPIN JP:
Overview: efficacy and safety of the rapid neuroleptization method with injectable haloperidol. Am J Psychiatry 1979; 136: 273–278.

73. THOMPSON C:
The use of high-dose antipsychotic medication. Br J Psychiatry 1994; 164: 448–458.

74. DAVIS JM, CHEN N:
Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004; 24: 192–208.

75. VOLAVKA J, COOPER T, CZOBOR P, BITTER I, MEISNER M, LASKA E et al.:
Haloperidol blood levels and clinical effects. Arch Gen Psychiatry 1992; 49: 354–361.

76. ADESOLA A, ANOZIE I, EROHUBIE P, JAMES B:
Prevalence and correlates of 'high dose' antipsychotic prescribing: findings from a hospital audit. Ann Med Health Sci Res 2013; 3: 62–65.

77. ROH D, CHANG JG, KIM CH, CHO HS, AN SK, JUNG YC:
Antipsychotic polypharmacy and high-dose prescription in schizophrenia: a 5-year comparison. Aust N Z J Psychiatry. 2014; 48: 52–60.

78. FLEISCHHACKER WW, UCHIDA H:
Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. Int J Neuropsychopharmacol 2014; 17: 1083–1093.

79. GALLEGO JA, BONETTI J, ZHANG J, KANE JM, CORRELL CU:
Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res 2012; 138: 18–28.

80. UCHIDA H, SUZUKI T, TAKEUCHI H, ARENOVICH T, MAMO DC:
Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis. Schizophr Bull 2011; 37: 788–799.

81. LEUCHT S, SAMARA M, HERES S, PATEL MX, WOODS SW, DAVIS JM:
Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr Bull 2014; 40: 314–326.

82. DOLD M, LI C, GILLIES D, LEUCHT S:
Benzodiazepine augmentation of antipsychotic drugs in schizophrenia: a meta-analysis and Cochrane review of randomized controlled trials. Eur Neuropsychopharmacol 2013; 23: 1023–1033.

83. GILLIES D, SAMPSON S, BECK A, RATHBONE J:
Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database Syst Rev 2013; Issue 4. Art. No.: CD003079.

84. FARDE L, NYBERG S:
Dosing determination for novel antipsychotics – a PET-based approach. Int J Psych Clin Pract 1998; 42: S39–S42.

85. TENBACK DE, VAN HARTEN PN, VAN OS J:
Non-therapeutic risk factors for onset of tardive dyskinesia in schizophrenia: a meta-analysis. Mov Disord 2009; 24: 2309–2315.

86. HAASE HJ, JANSSEN P:
The Action of Neuroleptic Drugs. A Psychiatric, Neurologic and Pharmacological Investigation. Amsterdam: North-Holland Publ. Co., 1965

87. JERMENDY G, BITTER I:
Antipszichotikus terápia és metabolikus szindróma. A Magyar Diabetes Társaság Metabolikus Munkacsoportja és a Pszichiátriai Szakmai Kollégium konszenzus-értekezlete (Antipsychotic treatment and metabolic syndrome. Consensus meeting of the Metabolic Working Group of the Hungarian Diabetes Society and the Hungarian Psychiatric Collegium). Psychiatr Hung 2005;20:312–315. (Article in Hungarian)

88. LEUCHT S, CORVES C, ARBTER D, ENGEL RR, LI C, DAVIS JM:
Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; 373: 31–41.

89. LEUCHT S, CIPRIANI A, SPINELI L, MAVRIDIS D, ÖREY D, RICHTER F et al.:
Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013; 382: 951–962.

90. CORRELL CU:
From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. Eur Psychiatry 2010; 25 Suppl 2: S12–S21.

91. TIIHONEN J, HAUKKA J, TAYLOR M, HADDAD PM, PATEL MX, KORHONEN P:
A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry 2011; 168: 603–609.

92. KANE JM, GARCIA-RIBERA C:
Clinical guideline recommendations for antipsychotic long-acting injections. Br J Psychiatry Suppl 2009; 52: S63–S67.

93. TIIHONEN J, MITTENDORFER-RUTZ E, MAJAK M, MEHTÄLÄ J, HOTI 3, JEDENIUS E et al.:
Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia. JAMA Psychiatry 2017; 74: 686–693.

94. BRISSOS S, VEGUILLA MR, TAYLOR D, BALANZÁ-MARTINEZ V:
The role of long-acting injectable antipsychotics in schizophrenia: a critical appraisal. Ther Adv Psychopharmacol 2014; 4: 198–219.

95. MILLAN MJ, ANDRIEUX A, BARTZOKIS G, CADENHEAD K, DAZZAN P, FUSAR-POLI P et al.:
Altering the course of schizophrenia: progress and perspectives. Nat Rev Drug Discov 2016; 15: 485–515.

96. KAHN RS, SOMMER IE, MURRAY RM, MEYER-LINDENBERG A, WEINBERGER DR, CANNON TD et al.:
Schizophrenia. Nat Rev Dis Primers 2015; 1: 15067.

97. GAEBEL W, RIESBECK M:
Are there clinically useful predictors and early warning signs for pending relapse? Schizophr Res 2014; 152: 469–477.

98. HOWES OD, KAPUR S:
A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). Br J Psychiatry 2014; 205: 1–3.

99. LEUCHT S, SAMARA M, HERES S, PATEL MX, FURUKAWA T, CIPRIANI A et al.:
Dose equivalents for second-generation antipsychotic drugs: the classical mean dose method. Schizophr Bull 2015; 41: 1397–1402.

100. ANDREASEN NC, PRESSLER M, NOPOULOS P, MILLER D, HO BC:
Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biol Psychiatry 2010; 67: 255–262.

101. 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: 97-106.

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