REVISÃO

Review of the efficacy of placebo in comparative clinical trials between typical and atypical antipsychotics

Revisão da eficácia do placebo nos ensaios clínicos que comparam antipsicóticos típicos e atípicos

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Abstract

Objective: *To review the efficacy of placebo in comparison with atypical and typical antipsychotics for the treatment of schizophrenia and schizoaffective disorder and to evaluate the pertinence of using placebo in clinical trials with antipsychotics.* ***Method:*** *Trials in which the atypical antipsychotics were compared with typical antipsychotics and placebo were included. A search was conducted using the terms "amisulpride", "aripiprazole", "clozapine", "olanzapine", "quetiapine", "risperidone", "sertindole", "ziprasidone" and "zotepine". Main efficacy parameters were calculated using the proportion of "events" (defined as a deterioration or lack of improvement by at least 20% in Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale) and the pooled relative risk with random effects, with their respective 95% confidence intervals. We also calculated the necessary sample sizes in studies in which the study drug is compared to a typical antipsychotic or placebo.* ***Results:*** *The pooled efficacy rates observed were 40.8%, 34.9% and 21.3% for the atypical antipsychotics, typical antipsychotics and placebo, respectively. One hundred and sixty six patients would have to be included when a new drug is compared with placebo if calculation is based on a difference of 20% found between the atypical antipsychotic and placebo and 2,054 if the difference sought were that found between the atypical antipsychotic and the typical antipsychotic, i.e. 6%. The estimated therapeutic failures would be 115 of the 166 patients when the study drug is compared with placebo, and 1,274 failures in the 2,054 patients when the study drug is compared to the typical antipsychotic.* ***Conclusions:*** *Placebo controlled studies may reduce the number of individuals exposed to the harmful effects of ineffective drugs.*

Descriptors: *Antipsychotic agents; Meta-analysis; Placebo effect; Schizoaffective disorder; Schizophrenia*

Resumo

Objetivo: *Revisar a eficácia do placebo em comparação com a dos antipsicóticos atípicos e típicos no tratamento da esquizofrenia e do transtorno esquizoafetivo, bem como avaliar a pertinência do uso do placebo nos ensaios clínicos com antipsicóticos.* ***Método:*** *Foram incluídos estudos nos quais os antipsicóticos atípicos foram comparados com antipsicóticos típicos e placebo simultaneamente. A pesquisa bibliográfica incluiu os termos "amisulprida", "aripiprazol", "clozapina", "olanzapina", "quetiapina", "risperidona", "sertindol", "ziprasidona" e "zotepina". Os principais parâmetros de eficácia foram a proporção de "eventos" (definidos como deterioração ou falta de melhora de pelo menos 20% na* Positive and Negative Syndrome Scale *ou* Brief Psychiatric Rating Scale*) e os riscos relativos combinados (efeitos randômicos), com seus respectivos intervalos de confiança de 95%. Foram também estimados os tamanhos de amostras nos estudos em que a droga pesquisada fosse comparada com um antipsicótico típico ou com placebo.* ***Resultados:*** *As taxas de eficácia combinada foram de 40,8%, 34,9% e 21,3%, respectivamente, para os antipsicóticos atípicos, antipsicóticos típicos e placebo. Cento e sessenta e seis pacientes teriam de ser incluídos quando a nova droga fosse comparada com placebo se os cálculos fossem baseados na diferença de 20% encontrada entre o antipsicótico atípico e placebo, ao passo que 2.054 teriam de ser incluídos se a diferença procurada fosse aquela encontrada entre o antipsicótico atípico e o antipsicótico típico, isto é, 6%. Os insucessos terapêuticos estimados seriam de 115 entre os 166 pacientes quando a droga em estudo fosse comparada com placebo, e de 1.274 entre os 2.054 pacientes quando fosse comparada com um antipsicótico típico.* ***Conclusões:*** *Os estudos controlados por placebo podem reduzir o número de indivíduos expostos aos efeitos prejudiciais de drogas ineficazes.*

Descritores: *Agentes antipsicóticos; Metanálise; Efeito placebo; Transtorno esquizoafetivo; Esquizofrenia*

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Introduction

In recent years, various novel drugs, referred to as atypical antipsychotics (AAs), have been put on the market. Despite being generally considered more effective, better-tolerated and safer than conventional or typical antipsychotics (TAs), they are still far from constituting the optimal treatment for schizophrenic and schizoaffective patients[1]. Since these are severe and frequently difficult to treat disorders, the minimum criteria required to define improvement in clinical trials to test the efficacy of antipsychotics generally consists of a reduction in symptoms of between only 20% to 40%, contrary to the treatment of other psychiatric disorders such as depression for which the generally accepted minimum drug response criterion is 50%[2].

The term 'atypical' was first introduced to describe clozapine, since its properties were found to be different from those of the older, conventional, or typical neuroleptics[3]. More recently, however, this term has been accepted as including characteristics as: 1) absence of hyperprolactinemia; 2) greater efficacy in treating positive and negative symptoms as well as symptoms of disorganization; and 2) absence of tardive diskynesia or dystonia after being administered chronically[4,5]. However, only clozapine seems to fulfill such criteria[6]. A broader definition of the term 'atypical' encompasses the drugs that have at least equal antipsychotic activity compared to conventional neuroleptics and produce no or fewer extrapiramidal side effects such as the AAs currently available (amisulpride, risperidone, olanzapine, ziprasidone, quetiapine, sertindol, zotepine and aripiprazol)[5].

Despite AAs purportedly broader spectrum and greater efficacy in improving negative, cognitive and mood symptoms, many reviews have yielded discrepant information about the comparative efficacy of the available AAs and the data seem not to support the assertions of unequivocal differential efficacy among them in the treatment of schizophrenia[7]. Moreover, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[8] showed a high dropout rate with AAs because of either inefficacy or intolerable side-effects. In the CATIE study, the TA perphenazine appeared similar to quetiapine, risperidone and ziprasidone in terms of efficacy, although perphenazine had more discontinuations because of extra-pyramidal symptoms (EPS).

Placebo-controlled trials are usually considered the gold standard method to prove efficacy and safety of new drugs, including antipsychotics. In non placebo-controlled trials, it is not possible to correctly estimate nonspecific treatment effects or the effect of the natural course of the disease on the final outcome. Because detecting clinically important differences between a new drug and the established agents may require unreachable large sample due to a variety of issues, active controlled trials are designed frequently to show that the effect of a new drug is equivalent but not necessarily superior to the effect of the currently available drugs[9]. As there are serious ethical considerations about placing patients on a placebo if effective treatments are available, ethicists consider that new drugs should be tested necessarily against an active agent under such circumstances[10]. The problem is that in many non-placebo controlled trials, there is no sufficient evidence that a new drug is more effective, or even as effective, as the active comparator. Thus, it is sometimes recommended for methodological reasons that, even when effective drugs exist, trials take advantage of at least three arms, one of which is a placebo arm[11].

Considering that: 1) the use of placebo in trials to evaluate the efficacy of antipsychotics in schizophrenia and schizoaffective disorder may appear ethically unjustifiable; 2) pharmacological treatments considered effective for these psychiatric disorders seem to have already been well-established; and 3) the use of placebo is believed to place the patients at unnecessary risk, we decided to conduct this review with the following goals in mind: 1) to evaluate the efficacy of placebo in comparison with AAs and TAs for the treatment of schizophrenia and schizoaffective disorder; and 2) based on the results of item 1, to evaluate the pertinence of the use of placebo in clinical trials with antipsychotics by calculating the sample sizes necessary in trials with and without the use of a placebo arm.

Method

1. Inclusion and exclusion criteria

Randomized trials involving any AAs compared with TAs for the treatment of schizophrenia and schizoaffective disorder were included in this review as long as they also included a placebo arm. Trials in which the AAs were compared with placebo alone or with an active control alone were not included, since our intention was to evaluate the intensity of the placebo effect in comparison with AAs and TAs simultaneously.

2. Search strategies

The following search methods were used. First, the databases Medline and Web of Science were consulted using the terms "amisulpride", "aripiprazole", "clozapine", "olanzapine", "quetiapine", "risperidone", "sertindole", "ziprasidone" and "zotepine" to identify any controlled trial in which the AA drugs were compared with a TA and placebo simultaneously. Next, the reference lists of review articles and meta-analyses were examined to identify possible studies not found during the online search. For example, we checked the reference lists of the latest systematic reviews carried out by the Cochrane Collaboration which involved AAs available in the market[12-19].

3. Analysis of efficacy data

The parameters of efficacy calculated were: 1) the proportion of "events" in the study and control groups; 2) the pooled relative risk with random effects, with their respective 95% confidence intervals; 3) the reduction in absolute risk (the difference in frequency between the study and control groups); and 4) the number needed to treat (NNT), which is the number of patients that need to be treated in order to prevent an event, and is calculated from the complement of the reduction in absolute risk[20,21]. A test of heterogeneity was performed to verify the variability of the combinations between the studies selected ($p > 0.05$).

"Event" was defined as a deterioration or lack of improvement, as shown by the failure to reduce Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) scores by at least 20% (or a higher minimum percentage improvement criterion provided by the study).

4. Analysis of sample size

To calculate the sample sizes required to carry out trials with and without a placebo arm, the data originated from the efficacy analysis were used. The calculations were performed considering a two-tailed alpha of 0.05 and a statistical power of 0.80. We also calculated the necessary sample sizes in studies in which the study drug was compared to a conventional antipsychotic or placebo, assuming that the drug under investigation was as effective as the AAs reviewed in this paper.

Results

1. Efficacy analysis

Table 1 summarizes the characteristics of the studies included in this review. Studies fulfilling inclusion criteria involved risperidone (n = 3)[22-24], olanzapine (n = 1)[25], quetiapine (n = 1)[26], zotepine (n = 1)[27] and aripiprazole (n = 1)[28]. It was not possible to include clozapine, since studies carried out with this drug involved patients who were refractory to conventional antipsychotics and no studies were found in which clozapine was compared simultaneously with placebo and a conventional antipsychotic. Similarly, no studies were found that compared ziprasidone with a TA and placebo simultaneously. One study[29] compared sertindole with haloperidol and placebo but did not provide response rates. With the exception of one study[27] that compared zotepine with chlorpromazine, all studies included haloperidol as the active comparator.

Table 2 summarizes the studies identified in which the AA drugs risperidone, olanzapine, quetiapine, zotepine and aripiprazole were compared with a TA and placebo. The observation periods varied from 4 to 8 weeks according to the type of AA studied. The pooled efficacy rates observed were 40.8%, 34.9% and 21.3% for the AAs, TAs and placebo, respectively. In this case, it was calculated that 7 patients would have to be treated with the TAs and 5 with the AA drugs (NNT) to avoid one therapeutic failure that would occur among those treated with placebo, over a period of 4-8 weeks.

2. Analysis of sample size

As shown in Table 3, 166 patients would have to be recruited when a new drug is compared with placebo if calculation is based on a difference of 20% found between the AA and placebo. Sample size increases 12-fold to 2,054 if the difference sought were that found between the AA and the TA, i.e. 6%. In both cases, there will be therapeutic failures, estimated at a total of 115 of the 166 patients when the study drug is compared with placebo, and 1,274 failures in the 2,054 patients when the study drug is compared to the TA. Eleven-fold more therapeutic failures are estimated to occur when the study drug is compared to a TA.

Discussion

Haloperidol and other TA drugs are effective in the treatment of psychoses. Nevertheless, based on the results of comparative studies, they would appear to be less effective than second-generation antipsychotics. At this point, two possibilities emerge: 1) the AAs are more effective than TAs; and 2) TAs are as effective as AAs; however, they have been used at inadequate doses in the trials. In this case, TA doses should be optimized.

According to a systematic review carried out by our group involving trials performed over the past 30 years on the blood levels of this drug, the efficacy of haloperidol was 55% in schizophrenia and schizoaffective disorder; therefore, the failure rate was only 45%[30]. Nevertheless, following the exclusion of patients with blood levels outside the suggested therapeutic window (8-30 ng/ml), efficacy increased to 62%, i.e. higher than that shown by AAs in the present review (41%). Although this comparison must be viewed with caution since it is based on studies carried out in different populations with different objectives, these findings are corroborated by the systematic review carried out by Geddes et al.[31]. The widely promulgated view that the new antipsychotics are superior to conventional drugs is questioned in the light of the following findings: 1) the AAs' have a similar effect to the conventional drugs at doses equivalent to ≤ 12 mg of haloperidol; and 2) the AAs cause fewer extrapyramidal effects; however, overall tolerability is similar between the two groups. The authors suggest that the conventional antipsychotics should remain as the first-line therapy; however, the atypical drugs constitute a valuable option when extrapyramidal effects are a problem for using a TA[31].

Based on the aforementioned data, we have concluded that development of the ideal antipsychotic is still far from having been achieved, justifying continuation of clinical trials investigation. Table 3 shows that this is not a simple task, since only one of the seven studies included in this analysis succeeded in demonstrating the superiority of the TA over placebo in the study period of 4-8 weeks, according to our own statistical analyses. These findings do not mean that conventional antipsychotics are ineffective; nevertheless, they are unable to demonstrate its efficacy in such a short period of time, probably because the placebo and other non-pharmacologic effects might be higher in schizophrenia than was usually perceived, varying between 20% and 50%[32].

In this review, the difference between placebo and conventional treatment, i.e. the treatment usually used as standard therapy in clinical trials of schizophrenia and schizoaffective disorder, was 14% in a 4-8 week period. This difference is estimated to be greater in long-term studies, since antipsychotic effects are slow to appear with the use of antipsychotics and the placebo effect tends to disappear. This consideration, however, becomes meaningless within this

Table 1 - Characteristics of the parallel, randomized, double-blind, controlled trials of atypical versus typical antipsychotics and placebo in the treatment of schizophrenia and related disorders

Author (year) *Drugs*	n AA/TA/P	Diagnostic criteria	Assessment of psychopathology	Improvement criteria	AA (mg)	TA (mg)	Duration (weeks)
1. Borison (1992)[22] *Risperidone vs. haloperidol*	12/12/12	DSM-III-R Schizophrenia	BPRS	≥ 20%	2-10	4-20	6
2. Chouinard (1993)[23] *Risperidone vs. haloperidol*	66/21/22	DSM-III-R Schizophrenia	PANSS	≥ 20%	2-16	20	8
3. Marder (1994)[24] *Risperidone vs. haloperidol*	96/43/65	DSM-III-R Schizophrenia	PANSS	≥ 20%	2-16	20	8
4. Beasley (1996)[25] *Olanzapine vs. haloperidol*	127/68/62	DSM-III-R	BPRS	≥ 40%	2.5-17.5	10-20	6
5. Arvanitis (1997)[26] *Quetiapine vs. haloperidol*	203/50/51	DSM-III-R	BPRS	≥ 40%	150-750	12	6
6. Cooper (2000)[27] *Zotepine vs. chlorpromazine*	53/53/53	DSM-III-R	BPRS	≥ 20%	150-300	300-600	8
7. Kane (2002)[28] *Aripiprazole vs. haloperidol*	204/104/106	DSM-IV	PANNS	≥ 30%	15-30	10	4

AA = atypical antipsychotic; TA = typical antipsychotic; P = placebo

Table 2 - Failure to achieve an improvement of at least 20-40% in the PANSS or BPRS scores in controlled trials of atypical versus typical antipsychotics and placebo*

A		Therapeutic failure				Absolute risk reduction	Relative risk		NNT
		Atypical antipsychotics		Placebo					
First author (year)	n	Events/n	Rates	Events/n	Rates		(95%CI)	p	(95%CI)
Borison (1992)[22]	**24**	5/12	41.7	12/12	100.0	58.3	0.44 (0.23-0.84)	0.03	**2**
Chouinard (1993)[23]	**88**	32/66	48.5	19/22	86.4	37.9	0.56 (0.42-0.76)	0.004	**3**
Marder (1994)[24]	**254**	96/189	50.8	51/65	78.5	27.7	0.65 (0.54-0.78)	0.0002	**4**
Beasley (1996)[25]	**189**	69/127	54.3	41/62	66.1	11.8	0.82 (0.65-1.04)	0.17	**8**
Arvanitis (1997)[26]	**254**	149/203	73.4	48/51	94.1	20.7	0.78 (0.70-0.87)	0.003	**5**
Cooper (2000)[27]	**106**	14/53	26.4	32/53	60.4	34.0	0.44 (0.27-0.72)	0.0009	**3**
Kane (2002)[28]	**310**	141/204	69.1	89/106	84.0	14.8	0.82 (0.73-0.93)	0.007	**7**
Global analysis	**1,225**	**506/854**	**59.2**	**292/371**	**78.7**	**19.5**	**0.70 (0.60-0.80)**	**0.0001**	**5**
B		**Typical antipsychotics**							
Borison (1992)[22]	**24**	9/12	75.0	12/12	100.0	25.0	0.76 (0.54-1.08)	0.22	**4**
Chouinard (1993)[23]	**43**	11/21	52.4	19/22	86.4	34.0	0.61 (0.39-0.94)	0.04	**3**
Marder (1994)[24]	**127**	43/62	69.4	51/65	78.5	9.1	0.88 (0.72-1.09)	0.33	**11**
Beasley (1996)[25]	**130**	36/68	52.9	41/62	66.1	13.2	0.80 (0.60-1.07)	0.18	**8**
Arvanitis (1997)[26]	**101**	40/50	80.0	48/51	94.1	14.1	0.85 (0.73-0.99)	0.07	**7**
Cooper (2000)[27]	**106**	24/53	45.3	32/53	60.4	15.1	0.75 (0.52-1.08)	0.17	**7**
Kane (2002)[28]	**210**	78/104	75.0	89/106	84.0	9.0	0.89 (0.78-1.03)	0.15	**11**
Global analysis	**741**	**241/370**	**65.1**	**292/371**	**78.7**	**13.6**	**0.85 (0.79-0.92)**	**0.0001**	**7**

** The patients who used placebo were controls both for the atypical (A) and for the typical antipsychotics (B).*
Test for heterogeneity: p = 0.007 (atypical versus placebo) and p = 0.67 (typical versus placebo).

context, since trials involving placebo in the treatment of psychoses usually have a maximum duration of eight weeks. Therefore, based on the evidence available, the conventional antipsychotics are associated with only a small effect when observed for a period of up to eight weeks. On the other hand, with the exception of clozapine, the new antipsychotics have so far failed to demonstrate a clear superiority in terms of efficacy[7].

There is intense debate with respect to the ethical appropriateness of placebo use in clinical trials on medical conditions for which an effective treatment has already been established. Nevertheless, deciding which treatment is effective is a complex issue, especially regarding mental disorders in which the nonspecific effects of treatments are high. This leads to a discussion on placebo use and its effect on sample size calculations.

There is an inverse relationship between the sample size and the effect size. If a drug under investigation is compared to placebo, the number of patients that need to be included is relatively small and, consequently, the number of non-responders will be small. On the other hand, active controlled trials require the inclusion of more patients due to the small expected difference between study's drug and the standard active treatment. Paradoxically, these studies result in a higher number of non-responders[33]. As shown in Table 3, 1,274 failures would be expected to occur if a new drug were compared with an active control (haloperidol or chlorpromazine), compared to 115 failures if the comparison were with placebo. This means that at least 11 times more patients would fail to be treated under blinded conditions.

Of note, participants are usually hospitalized during the entire duration of such trials; hence, under constant supervision. In addition, they generally receive other medications to control anxiety, agitation and insomnia. Different forms of psychosocial management are also permitted such as, for example, support psychotherapy, occupational therapy and group activities, as well as other forms of non-pharmacological interventions. Treatment may also be discontinued if ineffective. Therefore, hospitalized psychiatric patients using placebo are not in fact receiving "no treatment". Hospitalization itself removes patients from family environment and may largely contribute with recovery, as recent studies found that high levels of expressed emotion within the family of schizophrenic patients are highly anxiogenic and largely responsible for psychotic relapses[34].

In this review, haloperidol was similar to placebo in 5 out of 6 studies[22,24-26,28] and in the only study to show the superiority of haloperidol over placebo, statistical significance was minimal (p = 0.04)[23]. In the only study we found in which another TA, chlorpromazine, was used as active control for the atypical zotepine, no significant difference was detected between chlorpromazine and placebo[27].

In conclusion, placebo controlled studies, if used as a prerequisite to compare new drugs under investigation with standard therapies, may reduce the number of individuals exposed to the harmful effects of ineffective drugs[33]. Therefore, it would be desirable to reconsider the restrictions on the use of placebo in clinical trials with antipsychotics for the reasons given above, but also because, unlike other psychiatric disorders, the pharmacological arsenal available for the treatment of schizophrenia is far from ideal.

Table 3 - Calculation of required sample sizes based on the data from studies comparing atypical to typical antipsychotics and to placebo. The numbers between parentheses (second column) represent the proportions of successful responses to treatment

Drug under investigation	Efficacy of control	Estimated *n* for each group	Expected therapeutic failures
Compared to:	P (21%)	83 (P) + 83 (D) = 166 (T)	66 (P) + 49 (D) = **115**
Compared to:	TA (35%)	1,027 (D) + 1,027 (TA) = 2,054 (T)	606 (D) + 668 (TA) = **1,274**

P = placebo; D = drug under investigation; TA = typical antipsychotic; T = total
** Supposing that it is as effective as the AAs reviewed in this study (41%)*

Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Irismar Reis de Oliveira	UFBA	Acadia*** Astra-Zeneca*** Bristol*** Janssen*** Lilly*** Pfizer***	CNPq***	Astra-Zeneca* Janssen* Lundbeck* Servier*	---	Astra-Zeneca* Janssen*	---
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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UFBA = Universidade Federal da Bahia; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico.
For more information, see Instructions to Authors.

References

1. De Oliveira IR, Juruena MF. Treatment of psychosis: 30 years of progress. *J Clin Pharm Ther*. 2006;31(6):523-34.
2. de Oliveira IR, Dardennes RM, Amorim ES, Diquet B, de Sena EP, Moreira EC, de Castro-e-Silva EJ, Payan C, Fermanian J, Marcílio C. Is there a relationship between antipsychotic blood levels and their clinical efficacy? An analysis of studies design and methodology. *Fundam Clin Pharmacol*. 1995;9(5):488-502.
3. Siegfried SL, Fleischhacker W, Lieberman JA. Pharmacological treatment of schizophrenia. In: Lieberman JA, Murray RM, editors. *Comprehensive care of schizophrenia: a textbook of clinical management*. London: Martin Dunitz; 2001.
4. Robertson GS, Matsumura H, Fibiger HC. Induction patterns of Fos-like immunoreactivity in the forebrain as predictors of atypical antipsychotic activity. *J Pharmacol Exp Ther*. 1994;271(2):1058-66.
5. de Oliveira IR, Ribeiro MG, Fregoneze JB, de-Sena EP, de Castro e Silva E. Regional c-fos expression in rat brain may predict antipsychotic therapeutic window. *J Clin Psychopharmacol*. 2000;20(6):705-6.
6. Meltzer HY. Atypical antipsychotic drugs. In: Bloom FE, Kupfer DJ, editors. *Psychopharmacology: the fourth generation of progress*. New York: Raven Press; 1995.
7. Tandon R, Fleischhacker WW. Comparative efficacy of antipsychotics in the treatment of schizophrenia: a critical assessment. *Schizophr Res.* 2005;79(2-3):145-55.
8. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical antipsychotic trials of intervention effectiveness (CATIE) investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Eng J Med.* 2005;353(12):1209-23.
9. McMahon RP, Kelly DL, Boggs DL, Li L, Hu Q, Davis JM, Carpenter WT Jr. Feasibility of Reducing the Duration of Placebo-Controlled Trials in Schizophrenia Research. *Schizophr Bull*. 2008;34(2):292-301.
10. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Eng J Med.* 1994;331(6):394-8.
11. Streiner DL. Alternatives to placebo-controlled trials. *Can J Neurol Sci.* 2007;34(Suppl 1):S37-41.
12. Bagnall A, Lewis RA, Leitner ML. Ziprasidone for schizophrenia and severe mental illness. *Cochrane Database Syst Rev*. 2000;4:CD001945.
13. Mota NE, Lima MS, Soares BG. Amisulpride for schizophrenia. *Cochrane Database Syst Rev*. 2002;(2):CD001357.
14. Hunter RH, Joy CB, Kennedy E, Gilbody SM, Song F. Risperidone versus typical antipsychotic medication for schizophrenia. *Cochrane Database Syst Rev*. 2003;(2):CD000440.
15. Srisurapanont M, Maneeton B, Maneeton N. Quetiapine for schizophrenia. *Cochrane Database Syst Rev*. 2004;(2):CD000967.
16. Duggan L, Fenton M, Rathbone J, Dardennes R, El-Dosoky A, Indran S. Olanzapine for schizophrenia. *Cochrane Database Syst Rev*. 2005;(2):CD001359.
17. Lewis R, Bagnall AM, Leitner M. Sertindole for schizophrenia. *Cochrane Database Syst Rev*. 2005;(3):CD001715.
18. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. *Cochrane Database Syst Rev.* 2006;(2):CD004578.
19. DeSilva P, Fenton M, Rathbone J. Zotepine for schizophrenia. *Cochrane Database Syst Rev*. 2006;4:CD001948.
20. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Eng J Med.* 1998;318(26):1728-33.
21. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ.* 1995;310(6977):452-4.
22. Borison RL, Pathiraja AP, Diamond BI. Risperidone: clinical safety and efficacy in schizophrenia. *Psychopharmacol Bull*. 1992;28(2):213-8.
23. Chouinard G, Arnott W. Clinical review of risperidone. *Can J Psychiatry*. 1993;38(Suppl. 3):S89-95.
24. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry*. 1994;151(6):825-35.
25. Beasley CM Jr, Tollefson GD, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology*. 1996;14(2):111-23.
26. Arvanitis LA, Miller BG. Multiple fixed doses of «Seroquel» (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Seroquel Trial 13 Study Group. *Biol Psychiatry*. 1997;42(4):233-46.
27. Cooper SJ, Tweed J, Raniwalla J, Butler A, Welch C. A placebo-controlled comparison of zotepine versus chlorpromazine in patients with acute exacerbation of schizophrenia. *Acta Psychiatr Scand.* 2000;101(3):218-25.
28. Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, Ali MW. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 2002;63(9):763-71.
29. Zimbroff DL, Kane JM, Tamminga CA, Daniel DG, Mack RJ, Wozniak PJ, Sebree TB, Wallin BA, Kashkin KB. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. *Am J Psychiatry.* 1997;154(6)4:782-91.
30. de Oliveira IR, de Sena EP, Pereira EL, Miranda AM, de Oliveira NF, Ribeiro MG, de Castro-e-Silva E, Dardennes RM, Samuel-Lajeunesse B, Marcilio C. Haloperidol blood levels and clinical outcome: a meta-analysis of studies relevant to testing the therapeutic window hypothesis. *J Clin Pharm Ther*. 1996;21(4):229-36.
31. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*. 2000;321(7273):1371-6.
32. Quitkin FM. Placebos, drug effects, and study design: a clinician's guide. *Am J Psychiatry*. 1999;156(6):829-36.
33. Leon AC. Placebo protects subjects form nonresponse: a paradox of power. *Arch Gen Psychiatry*. 2000;57(4):329-30.
34. Pharoah FM, Mari JJ, Streiner D. Family intervention for schizophrenia. *Cochrane Database Syst Rev*. 2000;(2):CD000088.