# Haloperidol Dose When Used as Active Comparator in Randomized Controlled Trials With Atypical Antipsychotics in Schizophrenia: Comparison With Officially Recommended Doses

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***Objective:*** To determine the doses of haloperidol as a comparator drug in randomized controlled trials (RCTs) with atypical antipsychotics in patients with schizophrenia and to compare these doses with the officially recommended doses for haloperidol in the United States and the United Kingdom.

***Data Sources:*** We searched for RCTs conducted and published in English in full before January 2005 in which atypical antipsychotics were compared with haloperidol for the treatment of schizophrenia. We searched for Cochrane Reviews in which 1 of the following atypical antipsychotics was evaluated for the treatment of patients with schizophrenia, schizophreniform psychosis, or other primary psychosis: amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone. For the gap between the end point of inclusion of the studies in the Cochrane Reviews and January 2005, we electronically searched the Cochrane Central Register of Controlled Trials for any further RCTs in which atypical antipsychotics were compared with haloperidol for the same indication. Search terms used were *haloperidol* **and** *schizophren** and *haloperidol* **and** *psychotic**, as well as the names of the selected atypical antipsychotics for the years that were not covered by the Cochrane Reviews. For each study, the required dose and mean dose of haloperidol were compared with officially recommended doses of haloperidol in U.S. (Food and Drug Administration) and U.K. (*British National Formulary*) guidelines.

***Data Synthesis:*** In all of the included studies (N = 49), the midpoints of the required doses were above the midpoint of the official recommended doses in the United States and United Kingdom for moderately ill patients. In 94% (U.S.) and 80% (U.K.) of the studies, they were above the upper border of the recommended doses. Compared with recommended doses for severely ill patients in both the United Kingdom and United States (range, 6–15 mg daily), in 17 studies (35%) the mean actual used dose was above the upper dose border for severely ill patients (15 mg daily).

***Conclusions:*** Nearly all randomized clinical trials used haloperidol in doses that were higher than the official recommended doses for moderately ill or even severely ill patients. Therefore, it is probable that the results of the RCTs were affected by the high dose of haloperidol, hampering the interpretation of the effects of atypical antipsychotics in their comparison with haloperidol.

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Since the 1970s, haloperidol has been one of the most frequently prescribed antipsychotics worldwide. Since then, haloperidol has often been used as a comparator in randomized controlled trials (RCTs), including those investigating the atypical antipsychotics. In these RCTs, atypical antipsychotics were found not only to be equally as effective as haloperidol against positive symptoms (hallucinations and delusions) but also to have a more pronounced effect on the negative symptoms associated with schizophrenia and to have a lower incidence of extrapyramidal side effects than haloperidol.[1,2] However, many of these studies were criticized for the fact that haloperidol was used in doses higher than necessary to obtain an optimal effect, thus accounting for more side effects.[3]

The objective of our study was to determine the required dose ranges and the actual used doses of haloperi-

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dol as a comparator drug in RCTs set up to evaluate the efficacy of atypical antipsychotics in schizophrenia and to compare these doses with the officially recommended doses for haloperidol in the United States and the United Kingdom.

## METHOD

### Data Sources

First, we searched the Cochrane Library for published Cochrane Reviews and included the reviews in which 1 of the following atypical antipsychotics was evaluated for the treatment of patients with schizophrenia, schizophreniform psychosis, or other primary psychosis: amisulpride,[4] aripiprazole,[5] olanzapine,[6] quetiapine,[7] risperidone,[8] sertindole,[9] and ziprasidone.[10] Studies on clozapine were not included since this antipsychotic is specifically indicated for treatment of refractory patients.

Second, for the gap between the end point of inclusion of the studies in the Cochrane Reviews and January 2005, we electronically searched the Cochrane Central Register of Controlled Trials for any further RCTs in which atypical antipsychotics were compared with haloperidol for the same indication. The Cochrane Central Register of Controlled Trials incorporates results of group searches of MEDLINE (1966 onwards), EMBASE (1980 onwards), CINAHL (1982 onwards), PsycINFO (1974 onwards), PSYNDEX (1977 onwards), and LILACS (1982–1999). We included studies containing the terms *haloperidol* **and** *schizophren** and studies containing the terms *haloperidol* **and** *psychotic**, as well as the names of the selected atypical antipsychotics for the years that were not covered by the Cochrane Reviews. Therefore, we searched for studies with amisulpride from 2000 onwards, aripiprazole from 2003 onwards, olanzapine from 1999 onwards, quetiapine from 2003 onwards, risperidone from 2001 onwards, sertindole from 1999 onwards, and ziprasidone from 1999 onwards.

### Study Selection

Studies were eligible for inclusion in this review if they met the following inclusion criteria: amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole, or ziprasidone was evaluated; oral formulations of haloperidol were used as comparator drug; dosing information on the required dose (or dose range) of haloperidol according to the study protocol and/or the mean dose that was used in the RCT was published; the study population consisted of adult psychiatric patients aged 18 to 65 years, treated for schizophrenia, schizophreniform psychosis, or other primary psychosis; random treatment allocation was mentioned in the study; and studies were English-language and were published as full reports in peer-reviewed journals before January 2005.

In our review, we used the results of the quality assessment used to select RCTs for the Cochrane Reviews. The methodological quality of the additional RCTs included in this review was assessed by the first and second authors (G.W.K.H., E.R.H.) using the criteria described by Jadad et al.[11] This test gives evidence of the strength of the relationship between allocation concealment and direction of effect. Studies with a score of 3 or higher were rated as studies with good internal validity.

We manually examined potential papers to see if they met the inclusion criteria. All potentially relevant studies were individually assessed by both the first and second authors (G.W.K.H., E.R.H.), and, in case of discrepancies, consensus was obtained after discussion. If multiple papers were published from the same RCT, the first full report was selected.

### Patients

Patients were classified as inpatients or outpatients according to their status at the time of inclusion in the RCT. We also collected information on the number of patients who were included in the haloperidol arm of each RCT.

### Outcomes

The first outcome was the required dose or dose range of haloperidol according to the RCT protocol. In the case of a dose range, the midpoint required dose was calculated. The second outcome was the actual used dose, defined as the mean dose that was used in the RCT and, if available, accompanied by the standard deviation and dose range. If the mean used dose was not available, the median used dose was collected. Finally, the midpoint required dose and mean actual used dose were weighted for the number of patients included in the haloperidol arm of the studies.

### Official Dose Recommendations

For recommended doses in the United States, we used the registered U.S. dose ranges of haloperidol for adults as retrieved from official U.S. Food and Drug Administration (FDA) labeling (latest version, 1998)[12]: for moderate symptomatology, 1–6 mg daily (midpoint = 3.5 mg); for severe symptomatology and for chronic or resistant patients and "to achieve prompt control, higher doses may be required in some cases," 6–15 mg daily (midpoint = 10.5 mg).[12] For recommended doses for schizophrenia and other psychoses in the United Kingdom, we used dose ranges provided by the *British National Formulary* (BNF) 2005 edition[13]: for initial treatment, 3–9 mg daily (midpoint = 6 mg); for severely affected or resistant patients, 6–15 mg daily (midpoint = 10.5 mg); and "for resistant schizophrenia, up to 30 mg daily . . . , adjusted according to response to lowest effective maintenance dose."[13] Dose recommendations for the United States were collected back until 1971, and, for the United Kingdom, back until 1970. No change of dose recommendation was found in

Table 1. Randomized Controlled Trials (RCTs) Included in the Review

| Atypical Antipsychotic Under Investigation | RCTs From Cochrane Reviews | | RCTs From Cochrane Central Register of Controlled Trials | | Total | |
|---|---|---|---|---|---|---|
| | Identified | Included | Identified | Included | Identified | Included |
| Amisulpride | 19 | 8 | 11 | 0 | 30 | 8 |
| Aripiprazole | 10 | 2 | 7 | 1 | 17 | 3 |
| Olanzapine | 16 | 4 | 110 | 5 | 126 | 9 |
| Quetiapine | 12 | 5 | 8 | 0 | 20 | 5 |
| Risperidone | 20 | 13 | 66 | 5 | 86 | 18 |
| Sertindole | 2 | 1 | 4 | 1 | 6 | 2 |
| Ziprasidone | 7 | 2 | 21 | 0 | 28 | 2 |
| Both olanzapine and risperidone | 3 | 2 | 32 | 2 | 35 | 4 |
| Total | 89 | 37 | 259 | 14 | 348 | 51 |

the United States or the United Kingdom since the introduction of the atypical antipsychotics.

## RESULTS

From the Cochrane Reviews we identified 89 RCTs in which atypical antipsychotics were studied for the treatment of patients with schizophrenia, schizophreniform psychosis, or other primary psychosis. We excluded studies in which haloperidol was not the comparator drug (N = 40), in which no oral formulation of haloperidol was used (N = 2), for which no dosing information was available (N = 2), or that were not published in a peer-reviewed journal as a full report (N = 8). Eventually, we included 37 RCTs from the Cochrane Reviews (Table 1).

With our additional literature search, we identified 259 publications. Subsequently, we excluded studies in which no oral formulation of haloperidol was used (N = 11), that were not published in a peer-reviewed journal as a full report (N = 105), that were not RCTs (N = 78), that had been published previously (N = 35), that included patients not treated for schizophrenia or other psychotic disorders (N = 11), that investigated children or the elderly (N = 2), that were not published in English (N = 1), or that had a Jadad score lower than 3 (N = 2). Eventually, we included 14 additional RCTs, leading to a total of 51 RCTs in this review (Table 1).

Of these RCTs, 47 provided data on both the required dose and the actual used dose of haloperidol in the RCT. Two studies[14,15] did not provide information on the required daily dose; 2 other studies[16,17] did not provide information on mean actual used dose. Therefore, 49 studies provided data on required dose and 49 studies provided data on actual used dose (Table 2).

Weighted averages of the required daily dose and mean actual dose, respectively, of haloperidol were calculated for amisulpride (17.6 and 17.9 mg), aripiprazole (8.9 and 10.0 mg), olanzapine (12.4 and 12.0 mg), quetiapine (13.4 and 11.6 mg), sertindole (10.0 and 10.0 mg), ziprasidone (10.5 and 9.2 mg), and both risperidone and olanzapine (15.6 and 15.8 mg).

Compared with the officially recommended doses in the United States,[12] in 48 studies (98%) the midpoint required doses in the RCT protocol and in 46 studies (94%) the mean actual used doses were above the advised upper dose for moderate symptomatology (range, 1–6 mg daily) (Figure 1). Compared with recommended doses in the United Kingdom,[13] in 48 studies (98%) the required doses in the RCT protocol and in 39 studies (80%) the mean actual used doses were above the upper dose border for initial dosing (range, 3–9 mg daily). Compared with recommended doses for severely ill patients in both the United Kingdom[13] and the United States[12] (range, 6–15 mg daily), in 36 studies (73%) midpoint required dose ranges and in 26 studies (53%) mean actual used doses were above the mean recommended dose (10.5 mg daily). Furthermore, in 17 studies (35%), the mean actual used dose was above the upper dose border for severely ill patients (15 mg daily). From 1988 to 1994, weighted average required dose and weighted average actual used dose, respectively, were 17.3 mg and 18.8 mg; from 1995 to 1999, 12.6 mg and 11.9 mg; and from 2000 to 2004, 11.4 mg and 11.5 mg.

## DISCUSSION

In this review, we found that in more than 90% of all RCTs in which atypical antipsychotics were compared with haloperidol in patients with schizophrenia and other primary psychotic disorders, haloperidol was used in doses above the upper limit for the officially recommended dose range of haloperidol for moderately ill patients (U.S. recommendation) or for initial treatment (U.K. recommendations). Compared with the recommended dose for psychotic patients "severely affected" (U.K.) or with "severe symptomatology" (U.S.), we found that in 73% of the RCTs, the midpoint required doses and, in 53%, the mean actual used doses were above the mean recommended dose of 10.5 mg daily and, in 35% of studies, were even above the upper border of the recommended dose of 15 mg daily.

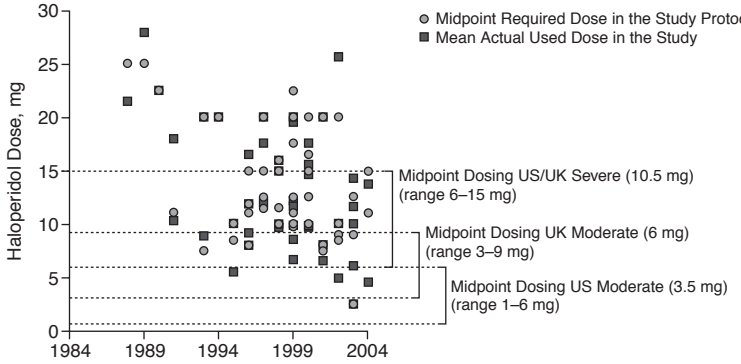
High doses of haloperidol are known for not being more effective (or for being even less effective) than low doses.[18] A meta-analysis found no evidence that high doses

**Table 2. Dose and Dose Range of Haloperidol as a Comparator Drug With Atypical Antipsychotics**

| Randomized Controlled Trial (RCT) | Inpatient or Outpatient | Year | Patients Treated With Haloperidol (N = 4259) | Required Daily Dose of Haloperidol in the RCT Protocol, mg | Mean Actual Used Dose of Haloperidol in the RCT, mg[a] |
|---|---|---|---|---|---|
| Amisulpride | | | | | |
| Pichot[27] | … | 1988 | 20 | 20–30 | 21.5 |
| Costa-e-Silva[28] | In | 1990 | 20 | 20–30 | 28 |
| Delcker[29] | In | 1990 | 20 | 5–40 | 22.5 |
| Möller[30] | In | 1997 | 96 | 20 | 20 |
| Speller[16] | In | 1997 | 31 | 3–20 | … |
| Puech[31] | … | 1998 | 64 | 16 | 16 |
| Carriere[32] | In | 2000 | 105 | 10–30 | 17.5 |
| Colonna[33] | In/out | 2000 | 118 | 5–20 | 14.6 (6.8) |
| Sum/weighted average | | | 474[b] | 17.6[c] | 17.9[c] |
| Risperidone | | | | | |
| Borison[34] | … | 1992 | 53 | 2–20 | 18.0 (1.4) |
| Claus[35] | In | 1992 | 21 | 2–20 | 10.3 (1.4) |
| Ceskova[36] | In | 1993 | 31 | 2–20 | 9.9 (4.2) |
| Chouinard[37] | In | 1993 | 21 | 20 | 20 |
| Min[38] | In | 1993 | 19 | 5–10 | 8.9 |
| Marder[13] | In | 1994 | 66 | 20 | 20 |
| Peuskens[39] | … | 1995 | 226 | 10 | 10 |
| Blin[40] | In | 1996 | 20 | 4–12 | 9.2 |
| Emsley[41] | … | 1999 | 84 | 1–16 | 5.6 |
| See[17] | In | 1999 | 10 | 15–30 | … |
| Wirshing[42] | In/out | 1999 | 33 | 5–30 | 19.4 (5.6) |
| Heck[43] | In | 2000 | 37 | 9–24 | 9.9 (range 3–18) |
| Cavallaro[44] | In | 2001 | 14 | 5–10 | 6.5 |
| Zhang[45] | In | 2001 | 37 | 20 | 20 |
| Csernansky[46] | Out | 2002 | 188 | 5–20 | 11.7 (5.0) |
| Green[47] | Out | 2002 | 30 | 2–16 | 5.0 (1.5) |
| De Sena[14] | Out | 2003 | 13 | … | 10.0 (median) |
| Marder[48] | Out | 2003 | 30 | 2–16 | 11.7 (5.0) |
| Sum/weighted average | | | 933[b] | 12.3[c] | 11.9[c] |
| Olanzapine | | | | | |
| Beasley[49] | In | 1996 | 69 | 10–20 | 16.4 (4.0) |
| Beasley[50] | In | 1997 | 81 | 10–20 | 17.6 |
| Tollefson[51] | … | 1997 | 660 | 5–20 | 11.8 (5.8) |
| Ishigooka[52] | … | 2001 | 84 | 4–12 | 8.0 (3.0) |
| Altamura[53] | … | 2002 | 11 | 5–20 | 12.3 (3.3) |
| de Haan[54] | In | 2003 | 12 | 2.5 | 2.5 |
| Rosenheck[55] | In | 2003 | 150 | 5–20 | 14.3 (4.6) |
| Keefe[56] | In | 2004 | 78 | 2–20 | 4.6 |
| Kinon[57] | In | 2004 | 48 | 10–20 | 13.8 |
| Sum/weighted average | | | 1193[b] | 12.4[c] | 12.0[c] |
| Quetiapine | | | | | |
| Arvanitis[58] | In | 1997 | 52 | 12 | 12 |
| Copolov[59] | In | 2000 | 227 | 6–16 | 8 |
| Emsley[60] | In | 2000 | 145 | 20 | 20 |
| Inada[61] | … | 2001 | 97 | 1.5–18 | 6.7 |
| Purdon[62] | In | 2001 | 12 | 10–20 | 15.5 (3.3) |
| Sum/weighted average | | | 533[b] | 13.4[c] | 11.6[c] |
| Sertindole | | | | | |
| Daniel[63] | Out | 1998 | 141 | 10 | 10 |
| Hale[64] | In | 2000 | 123 | 10 | 10 |
| Sum/weighted average | | | 264[b] | 10.0[c] | 10.0[c] |
| Ziprasidone | | | | | |
| Goff[65] | In/out | 1998 | 17 | 15 | 15 |
| Hirsch[66] | Out | 2002 | 153 | 5–15 | 8.6 |
| Sum/weighted average | | | 170[b] | 10.5[c] | 9.2[c] |
| Aripiprazole | | | | | |
| Daniel[67] | In | 2000 | 63 | 10 | 10 |
| Kane[68] | In | 2002 | 104 | 10 | 10 |
| Archibald[69] | … | 2003 | 433 | 7–10 | 10 |
| Sum/weighted average | | | 600[b] | 8.9[c] | 10.0[c] |
| Both olanzapine and risperidone | | | | | |
| Jones[70] | In | 1998 | 23 | 5–20 | 9.7 (4.2) |
| Purdon[71] | Out | 2000 | 23 | 5–20 | 9.7 (4.2) |
| Volavka[72] | In | 2002 | 37 | 10–30 | 25.7 (5.7) |
| Purdon[15] | Out | 2003 | 9 | … | 6.1 |
| Sum/weighted average | | | 92[b] | 15.6[c] | 15.8[c] |

[a]Values shown in parentheses are SD except where indicated otherwise.
[b]Value shown as sum.
[c]Value shown as weighted average.
Symbol: … = unknown.

**Figure 1. Midpoint Required Dose and Mean Actual Used Dose of Haloperidol as a Comparator Drug Compared With Atypical Antipsychotics**




affected the efficacy of haloperidol.[19] Although one can argue that 1 mg of haloperidol is not an optimal dose, the dose response curve of haloperidol begins to flatten out after 3.3 mg. High doses of haloperidol are associated with more side effects, particularly extrapyramidal side effects,[19] and may also induce negative symptomatology, explained by an excess of secondary negative symptoms associated with extrapyramidal side effects.[20,21]

In a meta-analysis of 52 RCTs that controlled for the higher-than-recommended dose of comparator drugs, only a modest advantage in favor of atypical antipsychotics in terms of extrapyramidal side effects remained.[18] However, differences in efficacy and overall tolerability between typical and atypical antipsychotics disappeared, suggesting that many of the perceived benefits of atypical antipsychotics are due to excessive doses of the comparator drug, e.g., haloperidol, used in the RCTs.[18]

In the official dose recommendations from the United States and the United Kingdom, the possibility of using (very) high doses of haloperidol is mentioned for severely ill or resistant patients, which theoretically might justify the higher dosing of haloperidol in the included RCTs. Indeed, audits of clinical practice sometimes find that higher-than-recommended doses are used in the real world.[22,23] However, one should also realize that severely ill patients were infrequently included in these RCTs because of strict inclusion criteria (e.g., no suicidal patients), and patients had to be able to give informed consent. Thus, study populations in RCTs differ from patients seen and treated in clinical practice. In various psychiatric disorders (depression, mania), it was found that only around 15% of patients treated in clinical practice would actually meet the strict inclusion criteria as applied in recent RCTs in these indications.[24–26]

Recommended doses are based on the current knowledge as obtained in RCTs for optimizing the balance between risk and benefits of drug treatment. As the majority of the RCTs in this review are efficacy trials, it is important that the dose of the active comparator is optimal. This review suggests that this is not the case and that the results from RCTs should be considered accordingly.

*Drug names:* aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

## REFERENCES


1. Meltzer HY. Outcome in schizophrenia: beyond symptom reduction. J Clin Psychiatry 1999;60(suppl 3):3–7
2. Kapur S, Remington G. Atypical antipsychotics [editorial]. BMJ 2000;321:1360–1361
3. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004;24:192–208
4. Mota NE, Lima MS, Soares BG. Amisulpride for schizophrenia. Cochrane Database Syst Rev 2002(2):CD001357
5. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. Cochrane Database Syst Rev 2004(2):CD004578
6. Duggan L, Fenton M, Dardennes RM, et al. Olanzapine for schizophrenia. Cochrane Database Syst Rev 2003(1):CD001359
7. Srisurapanont M, Maneeton B, Maneeton N. Quetiapine for schizophrenia. Cochrane Database Syst Rev 2004(2):CD000967
8. Hunter RH, Joy CB, Kennedy E, et al. Risperidone versus typical antipsychotic medication for schizophrenia. Cochrane Database Syst Rev 2003(2):CD000440
9. Lewis R, Bagnall A, Leitner M. Sertindole for schizophrenia. Cochrane Database Syst Rev 2000(2):CD001715
10. Bagnall A, Lewis RA, Leitner ML. Ziprasidone for schizophrenia and severe mental illness. Cochrane Database Syst Rev 2000(4):CD001945
11. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12
12. Haldol [prescribing information]. McNeil Pharmaceutical; 1998. Available at: http://www.fda.gov/cder/ogd/rld/15921s75.pdf. Verified April 6, 2006
13. Joint Formulary Committee. British National Formulary. 49th ed. London, England: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2005. Available at: http://www.bnf.org. Verified May 11, 2006
14. De Sena EP, Santos Jesus R, Miranda Scippa A, et al. Relapse in patients with schizophrenia: a comparison between risperidone and haloperidol. Rev Bras Psiquiatr 2003;25:220–223
15. Purdon SE, Woodward N, Lindborg SR, et al. Procedural learning in schizophrenia after 6 months of double-blind treatment with olanzapine, risperidone, and haloperidol. Psychopharmacology (Berl) 2003;169:390–397
16. Speller JC, Barnes TR, Curson DA, et al. One-year, low-dose neuroleptic

study of in-patients with chronic schizophrenia characterised by persistent negative symptoms: amisulpride v. haloperidol. Br J Psychiatry 1997;171:564–568
17. See RE, Fido AA, Maurice M, et al. Risperidone-induced increase of plasma norepinephrine is not correlated with symptom improvement in chronic schizophrenia. Biol Psychiatry 1999;45:1653–1656
18. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000;321:1371–1376
19. Davis JM, Chen N. Old versus new: weighing the evidence between the first- and second-generation antipsychotics. Eur Psychiatry 2005;20:7–14
20. Remington G, Chong SA, Kapur S. Distinguishing change in primary and secondary negative symptoms. Am J Psychiatry 1999;156:974–975
21. Barbui C, Garattini S. Clinical trials of new antipsychotics: a critical appraisal. Int Clin Psychopharmacol 1999;14:133–137
22. Edlinger M, Hausmann A, Kemmler G, et al. Trends in the pharmacological treatment of patients with schizophrenia over a 12 year observation period. Schizophr Res 2005;77:25–34
23. Remington G, Shammi CM, Sethna R, et al. Antipsychotic dosing patterns for schizophrenia in three treatment settings. Psychiatr Serv 2001;52:96–98
24. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? Am J Psychiatry 2002;159:469–473
25. Hofer A, Hummer M, Huber R, et al. Selection bias in clinical trials with antipsychotics. J Clin Psychopharmacol 2000;20:699–702
26. Storosum JG, Fouwels A, Gispen-de Wied CC, et al. How real are patients in placebo-controlled studies of acute manic episode? Eur Neuropsychopharmacol 2004;14:319–323
27. Pichot P, Boyer P. A controlled double-blind multi-centre trial of high dose amisulpride versus haloperidol in acute psychiatric states [in French]. Ann Psychiatr 1988;3:326–332
28. Costa-e-Silva JA. A comparative double-blind trial of amisulpride versus haloperidol in the treatment of acute psychotic disorders [in French]. Ann Psychiatr 1990;5:71–78
29. Delcker A, Schoon ML, Oczkowski B, et al. Amisulpride versus haloperidol in treatment of schizophrenic patients: results of a double-blind study. Pharmacopsychiatry 1990;23:125–130
30. Möller HJ, Boyer P, Fleurot O, et al. Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison with haloperidol. PROD-ASLP Study Group. Psychopharmacology (Berl) 1997;132: 396–401
31. Puech A, Fleurot O, Rein W. Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. The Amisulpride Study Group. Acta Psychiatr Scand 1998;98:65–72
32. Carriere P, Bonhomme D, Lemperiere T. Amisulpride has a superior benefit/risk profile to haloperidol in schizophrenia: results of a multicentre, double-blind study. The Amisulpride Study Group. Eur Psychiatry 2000;15:321–329
33. Colonna L, Saleem P, Dondey-Nouvel L, et al. Long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. Amisulpride Study Group. Int Clin Psychopharmacol 2000;15:13–22
34. Borison RL, Pathiraja AP, Diamond BI, et al. Risperidone: clinical safety and efficacy in schizophrenia. Psychopharmacol Bull 1992;28:213–218
35. Claus A, Bollen J, De Cuyper H, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. Acta Psychiatr Scand 1992;85:295–305
36. Ceskova E, Svestka J. Double-blind comparison of risperidone and haloperidol in schizophrenic and schizoaffective psychoses. Pharmacopsychiatry 1993;26:121–124
37. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993;13:25–40
38. Min SK, Rhee CS, Kim CE, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic patients: a parallel group double-blind comparative trial. Yonsei Med J 1993;34:179–190
39. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. Risperidone Study Group. Br J Psychiatry 1995;166:712–726
40. Blin O, Azorin JM, Bouhours P. Antipsychotic and anxiolytic properties of risperidone, haloperidol, and methotrimeprazine in schizophrenic patients. J Clin Psychopharmacol 1996;16:38–44
41. Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Risperidone Working Group. Schizophr Bull 1999;25:721–729
42. Wirshing DA, Marshall BD Jr, Green MF, et al. Risperidone in treatment-refractory schizophrenia. Am J Psychiatry 1999;156:1374–1379
43. Heck AH, Haffmans PM, de Groot IW, et al. Risperidone versus haloperidol in psychotic patients with disturbing neuroleptic-induced extrapyramidal symptoms: a double-blind, multi-center trial. Schizophr Res 2000;46:97–105
44. Cavallaro R, Mistretta P, Cocchi F, et al. Differential efficacy of risperidone versus haloperidol in psychopathological subtypes of subchronic schizophrenia. Human Psychopharmacology 2001;16:439–448
45. Zhang XY, Zhou DF, Cao LY, et al. Risperidone versus haloperidol in the treatment of acute exacerbations of chronic inpatients with schizophrenia: a randomized double-blind study. Int Clin Psychopharmacol 2001;16:325–330
46. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002;346:16–22
47. Green MF, Marder SR, Glynn SM, et al. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. Biol Psychiatry 2002;51:972–978
48. Marder SR, Glynn SM, Wirshing WC, et al. Maintenance treatment of schizophrenia with risperidone or haloperidol: 2-year outcomes. Am J Psychiatry 2003;160:1405–1412
49. Beasley CM Jr, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111–123
50. Beasley CM Jr, Hamilton SH, Crawford AM, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. Eur Neuropsychopharmacol 1997;7:125–137
51. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
52. Ishigooka J, Inada T, Miura S. Olanzapine versus haloperidol in the treatment of patients with chronic schizophrenia: results of the Japan multicenter, double-blind olanzapine trial. Psychiatry Clin Neurosci 2001;55:403–414
53. Altamura AC, Velona I, Curreli R, et al. Olanzapine in the treatment of paranoid schizophrenia. Eur Neuropsychopharmacol 2002;9(suppl 5): S297
54. de Haan L, van Bruggen M, Lavalaye J, et al. Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. Am J Psychiatry 2003;160:303–309
55. Rosenheck R, Perlick D, Bingham S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. JAMA 2003;290:2693–2702
56. Keefe RSE, Seidman LJ, Christensen BK, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry 2004;161:985–995
57. Kinon BJ, Ahl J, Rotelli MD, et al Efficacy of accelerated dose titration of olanzapine with adjunctive lorazepam to treat acute agitation in schizophrenia. Am J Emerg Med 2004;22:181–186
58. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biol Psychiatry 1997;42:233–246
59. Copolov DL, Link CGG, Kowalcyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636,'Seroquel') and haloperidol in schizophrenia. Psychol Med 2000;30:95–105
60. Emsley RA, Raniwalla J, Bailey PJ, et al. A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. Int Clin Psychopharmacol 2000;15:121–131
61. Inada T, Murasaki M. The drug induced extrapyramidal symptoms scale: differentiation of extrapyramidal symptom profiles and identification of favourable extrapyramidal symptoms profile of quetiapine in Japanese

patients. Eur Neuropsychopharmacol 2001;11(suppl 3):S265
62. Purdon SE, Malla A, Labelle A, et al. Neuropsychological change in patients with schizophrenia after treatment with quetiapine or haloperidol. J Psychiatry Neurosci 2001;26:137–149
63. Daniel DG, Wozniak P, Mack RJ, et al. Long-term efficacy and safety comparison of sertindole and haloperidol in the treatment of schizophrenia. The Sertindole Study Group. Psychopharmacol Bull 1998;34:61–69
64. Hale A, Azorin JM, Kasper S, et al. Sertindole improves both the positive and negative symptoms of schizophrenia: results of a phase III trial. Int J Psychiatry in Clinical Practice 2000;4:55–62
65. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998;18: 296–304
66. Hirsch SR, Kissling W, Bauml J, et al. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry 2002;63:516–523
67. Daniel DG, Saha AR, Ingenito GG, et al. Aripiprazole, a novel antipsychotic: overview of a phase II study result. Int J Neuropsychopharmacol 2000;3(suppl 1):S157
68. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002;63:763–771
69. Archibald DG, Manos G, Tourkodimitris S, et al. Reduction in negative symptoms of schizophrenia during long-term therapy with aripiprazole. Schizophr Res 2003;60(suppl 1):271
70. Jones B, Tollefson GD. Olanzapine versus risperidone and haloperidol in the treatment of schizophrenia. Schizophr Res 1998;29:150–151
71. Purdon SE, Jones BD, Stip E, et al. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. Arch Gen Psychiatry 2000;57:249–258
72. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Am J Psychiatry 2002;159:255–262