

Funding: This study was supported by unrestricted grants from the Society of American Gastrointestinal Endoscopic Surgeons and the Dutch Kidney Foundation.

Competing interest: None declared.

Ethical approval: This study was approved by the medical ethics committees of the university medical centres at Rotterdam and Nijmegen.

- 1 Ingelfinger JR. Risks and benefits to the living donor. *N Engl J Med* 2005;353:447-9.
- 2 Srivastava A, Tripathi DM, Zaman W, Kumar A. Subcostal versus transcostal mini donor nephrectomy: is rib resection responsible for pain related donor morbidity. *J Urol* 2003;170:738-40.
- 3 Yang SL, Harkaway R, Badosa F, Ginsberg P, Greenstein MA. Minimal incision living donor nephrectomy: improvement in patient outcome. *Urology* 2002;59:673-7.
- 4 Kok NF, Alwayn IP, Lind MY, Tran KT, Weimar W, Ijzermans JN. Donor nephrectomy: mini-incision muscle-splitting open approach versus laparoscopy. *Transplantation* 2006;81:881-7.
- 5 Dunker MS, Bemelman WA, Slors JF, van Duijvendijk P, Gouma DJ. Functional outcome, quality of life, body image, and cosmesis in patients after laparoscopic-assisted and conventional restorative proctocolectomy: a comparative study. *Dis Colon Rectum* 2001;44:1800-7.
- 6 Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 health survey. Manual and interpretation guide*. Boston, MA: Health Institute, New England Medical Centre, 1993.
- 7 Smets EM, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer* 1996;73:241-5.

- 8 Wolf JS Jr, Merion RM, Leichtman AB, Campbell DA Jr, Magee JC, Punch JD, et al. Randomized controlled trial of hand-assisted laparoscopic versus open surgical live donor nephrectomy. *Transplantation* 2001;72:284-90.
- 9 Simforoosh N, Basiri A, Tabibi A, Shakhssalim N, Hosseini Moghaddam SM. Comparison of laparoscopic and open donor nephrectomy: a randomized controlled trial. *Br J Urol Int* 2005;95:851-5.
- 10 Oyen O, Andersen M, Mathisen L, Kvarstein G, Edwin B, Line PD, et al. Laparoscopic versus open living-donor nephrectomy: experiences from a prospective, randomized, single-center study focusing on donor safety. *Transplantation* 2005;79:1236-40.
- 11 Lewis GR, Brook NR, Waller JR, Bains JC, Veitch PS, Nicholson ML. A comparison of traditional open, minimal-incision donor nephrectomy and laparoscopic donor nephrectomy. *Transpl Int* 2004;17:589-95.
- 12 Berends FJ, den Hoed PT, Bonjer HJ, Kazemier G, van Riemsdijk I, Weimar W, et al. Technical considerations and pitfalls in laparoscopic live donor nephrectomy. *Surg Endosc* 2002;16:893-8.
- 13 Lind MY, Liem YS, Bemelman WA, Dooper PM, Hop WC, Weimar W, et al. Live donor nephrectomy and return to work: does the operative technique matter? *Surg Endosc* 2003;17:591-5.
- 14 Perry KT, Freedland SJ, Hu JC, Phelan MW, Kristo B, Gritsch AH, et al. Quality of life, pain and return to normal activities following laparoscopic donor nephrectomy versus open mini-incision donor nephrectomy. *J Urol* 2003;169:2018-21.
- 15 Buell JF, Lee L, Martin JE, Dake NA, Cavanaugh TM, Hanaway MJ, et al. Laparoscopic donor nephrectomy vs open live donor nephrectomy: a quality of life and functional study. *Clin Transplant* 2005;19:102-9.
- 16 Wadstrom J. Hand-assisted retroperitoneoscopic live donor nephrectomy: experience from the first 75 consecutive cases. *Transplantation* 2005;80:1060-6.

(Accepted 25 May 2006)

doi 10.1136/bmj.38886.618947.7C

Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study

Jari Tiihonen, Kristian Wahlbeck, Jouko Lönnqvist, Timo Klaukka, John P A Ioannidis, Jan Volavka, Jari Haukka

Editorial by Kingdon

Department of Forensic Psychiatry, University of Kuopio, Niuvanniemi Hospital, FIN-70240 Kuopio, Finland
 J Tiihonen
professor and chairman

National Research and Development Centre for Welfare and Health (STAKES), Helsinki, Finland
 K Wahlbeck
research professor

Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki

J Lönnqvist
research professor

J Haukka
senior researcher

continued over

BMJ 2006;333:224-7

Abstract

Objective To study the association between prescribed antipsychotic drugs and outcome in schizophrenia or schizoaffective disorder in the community.

Design Prospective cohort study using national central registers.

Setting Community care in Finland.

Participants Nationwide cohort of 2230 consecutive adults hospitalised in Finland for the first time because of schizophrenia or schizoaffective disorder, January 1995 to December 2001.

Main outcome measures Rates of discontinuation of drugs (all causes), rates of rehospitalisation, and mortality associated with monotherapy with the 10 most commonly used antipsychotic drugs.

Multivariate models and propensity score methods were used to adjust estimates of effectiveness.

Results Initial use of clozapine (adjusted relative risk 0.17, 95% confidence interval 0.10 to 0.29), perphenazine depot (0.24, 0.13 to 0.47), and olanzapine (0.35, 0.18 to 0.71) were associated with the lowest rates of discontinuation for any reason when compared with oral haloperidol. During an average follow-up of 3.6 years, 4640 cases of rehospitalisation were recorded. Current use of

perphenazine depot (0.32, 0.22 to 0.49), olanzapine (0.54, 0.41 to 0.71), and clozapine (0.64, 0.48 to 0.85) were associated with the lowest risk of rehospitalisation. Use of haloperidol was associated with a poor outcome among women. Mortality was markedly raised in patients not taking antipsychotics (12.3, 6.0 to 24.1) and the risk of suicide was high (37.4, 5.1 to 276).

Conclusions The effectiveness of first and second generation antipsychotics varies greatly in the community. Patients treated with perphenazine depot, clozapine, or olanzapine have a substantially lower risk of rehospitalisation or discontinuation (for any reason) of their initial treatment than do patients treated with haloperidol. Excess mortality is seen mostly in patients not using antipsychotic drugs.

Introduction

Treatment algorithms for schizophrenia are currently based on outcome data from randomised controlled trials, but it is difficult to extrapolate data to wider community settings.¹ Most trials have a follow-up of a few



This is the abridged version of an article that was posted on bmj.com on 6 July 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38881.382755.2F>

months, so it is not known how the choice of antipsychotic drug affects the long term outcome of patients with a first episode of schizophrenia. Large scale observational studies could provide insight into this.

Several new second generation antipsychotic drugs have been used during the past two decades, and some have proved more efficacious than first generation drugs.² Second generation antipsychotics may be better tolerated and adherence to treatment may also be better, but this issue remains controversial.³⁻⁵ New drugs are also more expensive.

In Finland, the National Hospital Discharge Register can identify all patients treated in hospital since 1967. The diagnostic validity of schizophrenia is good.^{6,7} Information on mortality and cause of death is recorded by Statistics Finland, and all reimbursed drug prescriptions are registered by the Social Insurance Institution of Finland. By linking databases, we studied the relative effectiveness of the most frequently used antipsychotic drugs among patients in the community after their first admission to hospital for schizophrenia or schizoaffective disorder.

Methods

Assessment of outcomes

The outcome measures were mortality, discontinuation of drugs for any reason (death, hospitalisation, discontinuation, or switch to another antipsychotic drug), and rehospitalisation, a key indicator of relapse. In Finland, more than 90% of patients with schizophrenic psychosis are hospitalised, and non-elderly patients with schizophrenia are rarely hospitalised except during a relapse.⁶

Study population and data

We studied all people hospitalised because of a diagnosis of schizophrenia or schizoaffective disorder from 1 January 1995 to 31 December 2001 (the first hospital treatment period was considered as the index period); who had no previous discharge registered after hospitalisation due to schizophrenia-like psychosis; and who were 15-45 years old when the index hospitalisation began.

We obtained information on the study population by register linkage through personal identification

codes and data on the index hospitalisation from the discharge register. Dates and causes of death were obtained from Statistics Finland. Data on use of antipsychotic drugs came from a nationwide prescription register. See bmj.com for details.

For all patients studied, we obtained data on sex, age at index hospitalisation, year of index hospitalisation, duration of index hospitalisation (a proxy for baseline severity of illness), duration of all subsequent hospitalisations, and use of antipsychotic drugs after index hospitalisation. Drug purchasing data were used to calculate the duration of antipsychotic treatment. We determined the 10 most commonly used drugs and assigned patients who took only one of these drugs to the respective group. We assigned patients who took several antipsychotic drugs or uncommon drugs to a separate group (mixed or rare) and those who did not take drugs to another group. Oral haloperidol is the standard reference drug in clinical trials so we used patients who took this drug as the reference group.²

Data analysis

In the analysis of “all cause discontinuation of the initial drug,” we categorised patients according to the first drug used after their index hospital treatment (started within 30 days of discharge). Follow-up was continued until the drug was discontinued in community care for any reason (death, hospitalisation, discontinuation, or switch to another drug) or the end of the study period, whichever occurred first.

Rehospitalisation and death were attributed to the current (ongoing) antipsychotic drug. We calculated the incidence of rehospitalisation and death in the whole patient population. To obtain crude relative risks, we then compared these incidence figures for all drugs with the incidence figures for haloperidol.

We accounted for the impact of attrition during follow-up by calculating the relative risk of rehospitalisation for “initiated treatment” (monotherapy with a new antipsychotic drug started any time during the seven year follow-up) for each drug. This analysis is analogous to intention to treat analyses used in randomised controlled trials.

We divided each patient’s follow-up into contiguous periods of 30 days and counted the number of out

The Social Insurance Institution of Finland, Helsinki
T Klaukka
research professor

Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece

J P A Ioannidis
professor

New York University, New York, USA

J Volavka
professor emeritus

Correspondence to: J Tiihonen
jari.tiihonen@niuvafi

	No of relapses	Person years	Incidence	Crude relative risk (95% CI)	Adjusted relative risk (95% CI)	Fully adjusted relative risk (95% CI)	
Perphenazine depot	53	187	0.28	0.41 (0.29 to 0.59)	0.45 (0.32 to 0.65)	0.32 (0.22 to 0.49)	
Olanzapine	329	822	0.40	0.59 (0.45 to 0.75)	0.55 (0.43 to 0.72)	0.54 (0.41 to 0.71)	
Clozapine	336	804	0.42	0.61 (0.47 to 0.79)	0.53 (0.41 to 0.69)	0.64 (0.48 to 0.85)	
Chlorprothixene	79	146	0.54	0.79 (0.58 to 1.09)	0.83 (0.61 to 1.15)	0.64 (0.45 to 0.91)	
Thioridazine	115	201	0.57	0.84 (0.63 to 1.12)	0.82 (0.61 to 1.10)	0.70 (0.51 to 0.96)	
Perphenazine oral	155	327	0.47	0.69 (0.58 to 0.82)	0.78 (0.59 to 1.03)	0.85 (0.63 to 1.13)	
Risperidone	343	651	0.53	0.77 (0.60 to 0.99)	0.80 (0.62 to 1.03)	0.89 (0.69 to 1.16)	
Mixed or rare	775	1229	0.63	0.92 (0.73 to 1.17)	0.85 (0.67 to 1.08)	1.00 (0.78 to 1.28)	
Haloperidol oral	73	107	0.68	1.00	1.00	1.00	
Chlorpromazine	82	127	0.64	0.94 (0.69 to 1.29)	0.97 (0.71 to 1.33)	1.06 (0.76 to 1.47)	
Levomepromazine	52	63	0.82	1.21 (0.84 to 1.73)	0.82 (0.58 to 1.18)	1.09 (0.76 to 1.57)	
No antipsychotic drugs	2248	3362	0.67	0.98 (0.77 to 1.23)	1.01 (0.80 to 1.27)	1.16 (0.91 to 1.47)	

Relative risk of rehospitalisation by treatment. Adjusted for sex, calendar year, age at onset of follow-up, number of previous relapses, duration of first hospitalisation, and length of follow-up by a multivariate regression model alone (adjusted column) and by multivariate regression and the propensity score method (fully adjusted column)

Risk of all cause discontinuation (death, hospitalisation, discontinuation, or switch to another drug) of initial antipsychotic drug (started within 30 days of discharge after the hospital treatment period). Values are relative risk (95% confidence interval) unless otherwise indicated

Drug	Person years	Mean age (years)	Length of first hospitalisation (days)	Incidence of all cause discontinuation (/person years)			Adjusted analysis (patients on low dose haloperidol as reference)§		
				Discontinued*	Hospitalised†	Crude analysis	Adjusted analysis‡		
Clozapine	213	27.4	174.9	85	23	0.51	0.17 (0.12 to 0.24)	0.17 (0.10 to 0.29)	0.22 (0.07 to 0.71)
Perphenazine depot	38	34.9	95.7	30	1	0.82	0.27 (0.17 to 0.44)	0.24 (0.13 to 0.47)	0.11 (0.03 to 0.41)
Olanzapine	138	28.6	93.4	118	37	1.14	0.38 (0.26 to 0.54)	0.35 (0.18 to 0.71)	1.49 (0.44 to 6.77)
Risperidone	129	30.7	61.8	176	38	1.66	0.55 (0.39 to 0.78)	0.49 (0.33 to 0.74)	0.98 (0.38 to 2.50)
Chlorpromazine	25	31.0	65.0	48	12	2.41	0.80 (0.53 to 1.21)	0.56 (0.33 to 0.92)	0.50 (0.17 to 1.48)
Chlorprothixene	18	30.0	80.4	36	4	2.25	0.74 (0.48 to 1.17)	0.73 (0.41 to 1.28)	1.36 (0.44 to 4.18)
Thioridazine	30	32.1	52.3	50	10	2.03	0.67 (0.45 to 1.01)	0.75 (0.45 to 1.23)	1.51 (0.50 to 4.61)
Mixed or rare¶	180	31.8	80.9	410	60	2.62	0.87 (0.62 to 1.22)	0.80 (0.56 to 1.14)	1.51 (0.68 to 3.35)
Perphenazine oral	32	32.7	75.6	91	12	3.24	1.08 (0.74 to 1.57)	0.92 (0.58 to 1.46)	2.54 (0.86 to 7.46)
Haloperidol oral	12	31.5	53.8	32	5	3.01	1.00	1.00	1.00
Levomepromazine	3	32.3	57.2	17	2	6.44	2.14 (1.23 to 3.72)	1.94 (1.03 to 3.69)	3.51 (0.44 to 4.18)
No antipsychotic drug	2696	30.6	80.5	394**	265	-	-	-	-

Four patients not taking drugs died; no patients taking antipsychotic drugs died. End points of follow-up were all cause change in treatment status or the end of follow-up.

*No of patients who discontinued or switched their initial drug to another antipsychotic.

†No of patients who were hospitalised.

‡Adjusted for sex, calendar year, age at onset of follow-up, duration of first hospitalisation, and length of follow-up; also adjusted with propensity score method.

§Fully adjusted and stratified by median dose of haloperidol (8 mg/day) at discharge from index admission. Patients with a low dose of haloperidol (≤ 8 mg/day) form the reference group.

¶Patients taking several antipsychotic drugs or uncommon drugs (such as quetiapine, sertindole, and haloperidol depot injection).

**394 patients not taking drugs changed their treatment status (started taking antipsychotic drugs).

of hospital follow-up time periods and the number of rehospitalisations in each time period. We also determined drug usage during the 30 day periods. The 30 day periods were used as units for Poisson regression analysis to obtain crude estimates of the risk of discontinuation of the initially used drug, and the risk of rehospitalisation with current use of each drug versus current use of haloperidol. We adjusted estimates for background variables. Estimates were also adjusted for the propensity to start a specific treatment other than haloperidol. We evaluated the consistency between the results obtained with multivariate regression adjustment alone and with both multivariate and propensity score adjustment. Mortality was modelled similarly. See bmj.com for details.

Results

Study cohort

The cohort comprised 2230 patients (1383 men, 847 women). The median duration of index hospitalisation was 51 days (interquartile range 22-96). The mean age of patients was 30.7 years (SD 7.6), and the average length of follow-up was 3.6 years. In total, we recorded 4640 rehospitalisations and 84 deaths during follow-up. Young age, long duration of index treatment (≥ 90 days), and an increasing number of previous relapses were associated with increased risk of rehospitalisation ($P < 0.001$ for each variable; see bmj.com). The most commonly used antipsychotic drugs during the entire follow-up period are shown in the figure. Risperidone and chlorpromazine were used more often, and olanzapine, clozapine, and perphenazine depot were used less often as the initial drug in community care when compared with their use during the entire follow-up period. See bmj.com for details and doses of antipsychotic drugs.

Relative effectiveness: discontinuation of initial treatment

The table shows the all cause risk of stopping initial treatment started within 30 days of discharge from the

index hospitalisation. Clozapine, perphenazine depot, and olanzapine had the lowest rate of discontinuation for any reason.

Relative effectiveness: current use

Significantly decreased crude risks of rehospitalisation were associated with current use of perphenazine depot, olanzapine, clozapine, oral perphenazine, and risperidone (fig 1). In multivariate adjusted analyses and analyses that also considered the propensity score, the results for the first three drugs remained significant, with similar estimates of effect, but the results for oral perphenazine and risperidone were not significant. We found a significant interaction between sex and the effect of haloperidol on the risk of rehospitalisation (33 rehospitalisations in 71 person years in men; 40 rehospitalisations in 36 person years in women; $P < 0.001$), with a worse outcome among women using haloperidol. No other significant interactions were seen.

Relative effectiveness: initiated use

In the analyses of initiated use of drugs, the lowest adjusted risks of rehospitalisation were associated with perphenazine depot (-41% reduction in relative risk compared with haloperidol), clozapine (-28%), and olanzapine (-27%); see bmj.com.

Mortality

In total, 84 patients died during follow-up. We found no significant differences between drugs. However, mortality was more than 10 times higher in patients not taking drugs than in patients currently taking antipsychotic drugs: 75 patients not taking drugs died (3362 person years) and nine patients taking drugs died (4664 person years) (adjusted relative risk 12.3, 6.0 to 24.1, corresponding to population attributable risk of 83%, 68% to 91%). Twenty six suicides occurred in patients not taking drugs compared with one suicide in patients taking drugs (crude relative risk 36.1, 4.9-266; adjusted relative risk 37.4, 5.1 to 276). The corresponding figures for all unnatural deaths (suicides, violence, accidents) were 51 per 3362 person

years and five per 4664 person years (14.1, 5.6–35.4) and for all natural deaths 24 per 3362 person years and four per 4664 person years (8.3, 2.9–24.0).

Discussion

Linking national databases of mortality, drug purchasing, and hospital treatment enabled us to study the effectiveness of antipsychotic treatment in the wide community by using mortality, rehospitalisation rates, and discontinuation of drugs for any reason as the outcome measures. First and second generation antipsychotic drugs varied greatly in terms of treatment adherence and effectiveness in this patient population. Patients treated with perphenazine depot, clozapine, or olanzapine had a lower risk of rehospitalisation or all cause discontinuation of their initial treatment than patients treated with haloperidol.

Limitations and strengths of our study

Observational studies may overestimate the size of treatment effects compared with randomised controlled trials. The lower rate of discontinuation and risk of rehospitalisation associated with certain antipsychotic drugs could be attributable to patient selection (patients who received these drugs were more compliant and less severely ill than other patients). Our main findings were that perphenazine depot and clozapine had the lowest risk of all cause discontinuation and rehospitalisation. Since perphenazine depot is used mostly in patients with the worst adherence to drug treatment (those who do not comply with oral medication), and clozapine is used only in treatment resistant patients (the most severely ill), it is unlikely that selection bias could explain the better outcome associated with these drugs.

Discontinuation of treatment

Patients who started taking clozapine, perphenazine depot, or olanzapine within 30 days of their first hospitalisation had the lowest risk of stopping the initial treatment for any reason. In a recent meta-analysis of randomised trials comparing haloperidol with second generation antipsychotics, high haloperidol doses (> 12 mg/day) were associated with a poor outcome, but no substantial differences were seen between drugs at haloperidol doses ≤ 12 mg/day.³ The median dose of haloperidol used in our study was 8 mg, well within the recommended optimal dose (6–12 mg/day). The relative risks of all cause discontinuation for clozapine and perphenazine depot were similar in an analysis stratified by median dose of haloperidol at discharge (patients taking low dose haloperidol were used as reference), but the confidence intervals were wider because of a smaller number of patients in the reference group.

Rehospitalisation

Initiated and current use of perphenazine depot, olanzapine, and clozapine were associated with the lowest risk of rehospitalisation, and patients who took these three drugs had a 27–68% lower risk of rehospitalisation than patients who took haloperidol. Depot injections of the first generation antipsychotic perphenazine were associated with the lowest risk of rehospitalisation. Second generation antipsychotics are much more expensive than first generation drugs.

What is already known on this topic

Guidelines for treating schizophrenia are mainly based on randomised controlled trials of selected patients with limited follow-up

How well these data can be applied to community settings and how the choice of antipsychotic drug affects long term outcome are unclear

What this study adds

The effectiveness of first and second generation antipsychotics varies greatly in a real world setting

Patients treated with perphenazine depot, clozapine, or olanzapine have a lower risk of rehospitalisation or all cause discontinuation of their initial treatment than patients treated with haloperidol

Excess mortality is seen mostly in patients not taking antipsychotic drugs

A recent large randomised study compared four second generation antipsychotics with first generation drugs and found that only olanzapine had a slightly better outcome than oral perphenazine.⁸

Mortality

The different drugs had no statistically significant effects on mortality, but the low number of deaths yielded low statistical power to detect such differences. Patients who currently took any antipsychotic drug had decreased mortality compared with the no treatment group. However, not using antipsychotic drugs may be a marker of other conditions that affect the risk of mortality.

Thanks to Aija Räsänen for excellent secretarial assistance.

Contributors: See bmj.com.

Funding: Annual EVO financing (special government subsidy) from Niuvanniemi Hospital, Kuopio, Finland.

Competing interests: None declared.

Ethical approval: No ethical committee approval needed for a register based study. Approval obtained from all institutions involved and from Ministry of Health and Social Welfare.

- 1 Thornley B, Adams C. Content and quality of 2000 controlled trials in schizophrenia over 50 years. *BMJ* 1998;317:1181-4.
- 2 Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 2003;60:553-64.
- 3 Geddes JR, Freemantle N, Harrison P, Bebbington PE. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ* 2000;321:1371-6.
- 4 Geddes J. Prevention of relapse in schizophrenia. *N Engl J Med* 2002;346:56-8.
- 5 Leucht S, Wahlbeck K, Hamann J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* 2003;361:1581-9.
- 6 Isohanni M, Makikyro T, Moring J, Rasanen P, Hakko H, Partanen U, et al. A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish national birth cohort. Clinical and research diagnoses of schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 1997;32:303-8.
- 7 Suvisaari JM, Haukka JK, Tanskanen AJ, Lönnqvist JK. Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. *Arch Gen Psychiatry* 1999;56:733-40.
- 8 Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005;353:1209-23.

(Accepted 14 April 2006)

doi 10.1136/bmj.38881.382755.2F