ORIGINAL INVESTIGATION

Stefan Leucht · Stefan Wagenpfeil ·
Johannes Hamann · Werner Kissling

Amisulpride is an "atypical" antipsychotic associated with low weight gain

Abstract *Rationale:* It is possible that amisulpride, with its unique receptor binding profile, is not associated with significant weight gain, a serious side effect of most "atypical" antipsychotic drugs. While most "atypicals" have a high affinity for both dopamine and serotonin receptors, amisulpride has only dopamine receptor action. *Objectives:* To analyse the weight gain associated with amisulpride. *Methods:* A pooled database of prospective randomised amisulpride studies was analysed. The mean weight gain after 10 weeks of treatment was estimated by regression analysis. *Results:* Eleven studies with a total of 1422 patients were pooled, providing 1392 patients who were eligible for evaluation. In the main analysis of all effective doses (50–1200 mg/day) the mean weight gain associated with amisulpride at 10 weeks was 0.8 kg, 95% CI (0.48–1.18). Linear regression showed no dependence of weight gain on daily dose levels (*P*=0.7). When patients with mean daily doses below 400 mg/day were excluded in a sensitivity analysis, the mean weight gain at ten weeks was again 0.80 kg, 95% CI (0.47–1.16) with *n*=874. The mean weight gain at study endpoints in 1-year studies was 1.4 kg, 95% CI (0.85–1.90), *n*=548. *Conclusion:* Amisulpride is an atypical antipsychotic associated with low weight gain.

Keywords Amisulpride · Weight gain · Antipsychotic drugs · Side effects

S. Leucht (✉) · J. Hamann · W. Kissling
Department of Psychiatry and Psychotherapy,
Klinikum rechts der Isar der Technischen Universität München,
Ismaningerstrasse 22, 81675 München, Germany
e-mail: Stefan.Leucht@lrz.tum.de

S. Leucht
The Zucker Hillside Hospital,
Kaufmann Building,
75–59 263rd Street, Glen Oaks, NY 11004, USA

S. Wagenpfeil
Institute of Medical Statistics and Epidemiology,
Technische Universität München,
Ismaningerstrasse 22, 81675 München, Germany

Introduction

The new generation of so-called "atypical" antipsychotics is increasingly becoming the principal medication for patients with schizophrenia. Amisulpride is a unique drug in this group. Whereas most of the other new generation antipsychotics have a high affinity for both dopamine and serotonin receptors, amisulpride is a selective dopamine receptor antagonist with high affinity for both D_3 and D_2 receptors (Perrault et al. 1996; Scatton et al. 1997). It has been shown in animal studies (Schoemaker et al. 1997), and also in humans (Bressan et al. 2003), that amisulpride has selectivity for mesolimbic over striatal dopamine mechanisms. This selectivity probably explains why, like the other new generation drugs, amisulpride induces fewer extrapyramidal side effects than high-potency conventional antipsychotics. At low doses it preferentially blocks presynaptic dopamine autoreceptors (Schoemaker et al. 1997). This effect leads to an enhancement of dopamine transmission and may explain why amisulpride was found to be more effective than placebo for patients with predominantly negative symptoms (Leucht et al. 2002). In addition, amisulpride has been shown to be more effective for the treatment of negative symptoms than conventional antipsychotics (Leucht et al. 2002; Mota Neto et al. 2003). It is therefore considered an "atypical" antipsychotic by influential treatment guidelines (NICE 2002), although this concept is difficult to define (Reynolds 1997) and should be regarded as a continuum rather than a dichotomous classification of antipsychotics.

There is a lot of concern about the potential of the new drugs for inducing weight gain. Obesity and weight gain are a threat to health, because they have been associated with hypertension, type II diabetes, stroke and certain kinds of cancer. The weight gain risk associated with a number of new generation antipsychotics was recently summarized in an influential meta-analysis by Allison and colleagues (Allison et al. 1999). Since amisulpride was not included in Allison's report, the aim of the present study was to fill this gap. Amisulpride's negligible

affinity for serotonin and histamine receptors involved in weight gain (Allison et al. 1999) suggested that it is unlikely to have major effects on body weight.

Materials and methods

Original patient data from all randomised studies of the manufacturer's amisulpride database available at the start of the project were used for the analysis. Important design features are summarised in Table 1 and have been reported in previous reviews (Leucht et al. 2002; Mota Neto et al. 2003). A number of older, mostly small studies did not provide weight data and were thus not included (Klein et al. 1985; Delcker et al. 1990; Pichot and Boyer 1988, 1989; Rüther et al. 1988; Costa e Silva 1989; Ziegler 1989; Saletu et al. 1994; Boyer et al. 1995). In short, with one exception (Colonna et al. 2000, randomized, open trial), all trials included were randomized and double blind. They lasted from 4 weeks to 1 year (median 12 weeks). The patients' weight was measured at baseline and then usually again at each study visit. DSM-III-R or DSM-IV were used as diagnostic criteria in all trials. Seven studies (n=1151; Möller et al. 1997; Puech et al. 1998; Wetzel et al. 1998; Peuskens et al. 1999; Carrière et al. 2000; Colonna et al. 2000; Sèchter et al. 2002) were carried out on patients with positive symptoms of schizophrenia or schizophreniform disorder and used amisulpride doses between 100 mg/day and 1200 mg/day. Four studies (n=271; Paillère-Martinot et al. 1995; Loo et al. 1997; Speller et al. 1997; Danion et al. 1999) examined patients with schizophrenia and predominant negative symptoms and few positive symptoms. In these studies, amisulpride doses between 50 and 300 mg/day were effective (Leucht et al. 2002).

We applied the regression analysis setting of Allison and colleagues (Allison et al. 1999) to estimate the average weight gain after 10 weeks of treatment with amisulpride. However, a more precise analysis was possible because, contrary to the study of Allison and his colleagues, individual patient data were used. A one-sample t-test was used in order to assess weight gain, and linear regression for the dependence of weight gain on dosage. In a sensitivity analysis, patients with mean amisulpride doses below 400 mg/day were excluded.

In addition to the regression analysis, the following values were indicated: The mean maximum weight gain at any point in the studies and the mean weight gain at study endpoints (last observation carried forward—LOCF). Long-term weight gain was assessed by pooling the last evaluations in 1-year studies (LOCF). Furthermore, to obtain weight gain estimates after 6 and 12 months, conservative completer analyses including all patients with an assessment between 152 and 212 days (mean 182 days) and between 320 and 410 days (mean 364 days), respectively, were undertaken. These time windows were chosen to have large enough samples, because in long-term trials patients often do not have visits at exactly the preplanned time points. This was more frequently the case at 12 months than at 6 months, so that a larger window had to be chosen for the latter time point. Quantitative measures are supplemented with 95% confidence intervals (CI). P-values are subject to a two-sided significance level of 0.05. Statistical analyses were conducted using SPSS, version 11.5.

Results

For 1392 [886 male, 506 female, age 36.4 95% CI (35.8–36.9)] out of 1422 patients the body weight at baseline and at least one later study visit was available and could thus be included in the analysis. Their mean weight at baseline was 70.3 kg, 95% CI (69.6–71.1). The mean daily amisulpride dose was 450.1, 95% CI (435.1–465.1). Amisulpride treatment was associated with a statistically significant ($P<0.001$), but relatively low weight gain: the estimated weight gain after 10 weeks of treatment was 0.80 kg, 95% CI (0.48–1.18). Linear regression showed no dependence of weight gain on daily dose levels ($P=0.7$). Excluding patients with mean daily doses <400 mg in a sensitivity analysis, the mean daily

Table 1 Description of studies included in the database. *AMI* amisulpride, *HAL* haloperidol, *PBO* placebo, *FLU* flupentixol, *RCT* randomised controlled trial, *DB* double-blind, *MC* multi-center, *TC* two-center, *FID* fixed dose, *FLD* flexible dose, *PW* premature withdrawal, *M* month

Study	Design	Amisulpride daily dose (mg) and comparator drug	Sample size	Study duration (weeks)	Weight assessment at weeks
Möller et al. (1997)	RCT, DB, MC, FID	AMI 800, HAL 20	95, 96	6	0, 1, 2, 3, 4, 5, 6 PW
Wetzel et al. (1998)	RCT, DB, MC, FID[a]	AMI 1000/600[a], FLU 25/15[a]	70, 62	6	0, 1, 2, 3, 4, 5, 6, PW
Puech et al. (1998)	RCT, DB, MC, FID	AMI (100; 400; 800; 1200), HAL 16	(61; 64; 65; 65), 64	4	0, 1, 2, 3, 4, PW
Colonna et al. (2000)	RCT, open, MC, FLD	AMI 200–800, HAL 5–20	370, 118	12 months	0, 1, 2, M1, M3, M6, M9, M12, PW
Carrière et al. (2000)	RCT, DB, MC, FLD	AMI 400–1200, HAL 10–30	94, 105	4 months	0, 1, 2, 4, M2, M4, PW
Peuskens et al. (1999)	RCT, DB, MC, FID	AMI 800, RIS 8	115, 113	8	0, 1, 2, 3, 4, 6, 8, PW
Sèchter et al. (2002)	RCT, DB, MC, FLD	AMI 400–1000, RIS 4–10	152, 158	12 months[b]	0, 1, 2, 3, 4, 6, 8, M3, M4, M5, M6, M9, M12, PW
Danion et al. (1999)	RCT, DB, MC, FID	AMI (50; 100), PBO	(84;75), 83	12	0, 2, 4, 8, 12, PW
Loo et al. (1997)	RCT, DB, MC, FID	AMI 100, PBO	69, 72	6 months	0, 1, M1, M2, M3, M4, M5, M6, PW
Paillère-Martinot et al. (1995)	RCT, DB, MC, FID	AMI 50, PBO	14, 13	6	0, 6, PW
Speller et al. (1997)	RCT, DB, TC, FLD	AMI "low-dose", HAL "low-dose"	29, 31	12 months	0, 6, M3, M6, M9, M12, PW

[a] All patients were started on the higher dose which could later be reduced
[b] The original publication reported 6 months results, but there was a 12-month extension

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Table 2 Sensitivity analysis of long-term weight gain excluding patients with mean amisulpride doses below 400 mg/day. *n* number of patients, *LOCF* last observation carried forward, the numbers in brackets are the limits of the 95% confidence intervals

	Endpoint (LOCF) analysis of all 1-year studies	6 months window	12 months window
n	367	245	187
Mean weight gain (kg)	1.29 (0.68–1.90)	1.27 (0.63–1.91)	2.29 (1.25–3.33)
Mean daily dose (mg)	568 (551–584)	560 (542–579)	568 (547–590)
Mean duration of treatment (days)	252 (238–266)	182 (range: 152–212)	364 (range: 320–410)

amisulpride dose in the remaining 874 patients was 624.4, 95%CI (610.9–637.9), and the estimated weight gain after 10 weeks treatment with amisulpride was 0.80 kg, 95% CI (0.47–1.16).

The mean maximum weight gain at any time point in the studies was 2.5 kg, 95% CI (2.3–2.7), and the mean weight gain at study endpoints (LOCF) was 1.0 kg, 95% CI (0.8–1.3), mean duration of treatment 143 days, 95% CI (135–150), *n*=1392. Excluding patients with mean daily doses below 400 mg did not change these results (*n*=874, mean maximum weight gain 2.5 kg, 95% CI (2.3–2.7); mean weight gain at study endpoints 1.0 kg, 95% CI (0.7–1.3); mean duration of treatment 139 days, 95% CI (130–148).

Pooling the results of all 1-year studies (*n*=548), the mean weight gain at study endpoints (LOCF) was 1.37 kg, 95% CI (0.85–1.90); mean duration of treatment 256 days, 95% CI (245–268), mean daily dose 466 mg, 95% CI (449–483). The observed cases (*n*=402) in the 6-month window (152–212 days, mean 182) had a mean weight gain of 1.40 kg, 95% CI (0.86–1.94); mean daily dose 428 mg, 95% CI (407–448). The observed cases (*n*=311) in the 12-month window (320–410 days, mean 364 days) had a mean weight gain of 2.15 kg, 95% CI (1.3–3.0); mean daily dose 430 mg, 95% CI (405–454). Table 2 shows that even in these long-term analyses, excluding patients with mean doses below 400 mg/day did not change the results to any substantial degree.

Discussion

This weight gain analysis fills a gap in the process of evidence-based decision making in the treatment of schizophrenia. It shows that amisulpride is associated with only a slight weight gain of approximately 0.8 kg within 10 weeks across the entire effective dose range. If we compare amisulpride with the list of new generation antipsychotics analysed by Allison and colleagues (1999) it is associated with a higher 10-week weight gain than ziprasidone (0.04 kg), and a lower weight gain than risperidone (2.10 kg), sertindole (2.92 kg), olanzapine (4.15 kg) and clozapine (4.45 kg). Compared to these numbers, even the long-term weight gain of 2.15 kg after one year of treatment with amisulpride based on our conservative completer analysis underlines the quite favourable weight profile of this antipsychotic.

Other new generation antipsychotics that were not included in the report by Allison et al. 1999 are quetiapine and aripiprazole. According to a previous review, the mean weight gain in the quetiapine groups in its pivotal randomised double-blind 6-week trials ranged between 1.8 kg and 5.5 kg (Taylor and McAskill 2000). In a summary of controlled and uncontrolled trials, Rak et al. 2000 reported a mean weight gain of 2.1 kg after 5–6 weeks and of 2.8 kg after 9–12 months. However, in a recent analysis of a cohort of 427 patients on strict monotherapy, quetiapine appeared to have weight-neutral effects in the long run (Brecher 2000). Concerning aripiprazole, Jody et al. (2002) reported a mean weight increase of 0.7 kg at endpoint (LOCF) in five 4- to 6-week studies. The results of two long-term studies were conflicting, because in a haloperidol controlled study the mean weight gain of the observed cases after 1 year was approximately 2.6 kg (LOCF analysis 1.1 kg), whereas in a 6-month, olanzapine-controlled study there was a weight loss in the aripiprazole group of 0.8 kg (LOCF 0.9 kg; Jody et al. 2002). The higher mean baseline weight of the aripirazole group in the olanzapine-controlled study (87.4 kg) than in the haloperidol-controlled study (74.1 kg) might account for these differences.

A methodological strength of our analysis is that since all individual patient data were available, our estimates are presumably somewhat more precise than those of the meta-analysis by Allison and colleagues (1999). Without having original patient data available, the latter authors had to make a number of assumptions and extrapolations, e.g. when the studies did not report means or standard deviations, which then had to be estimated for their calculations. Furthermore, their regression model was probably less exact, because the mean weight change is often indicated only on an LOCF basis in publications. Given the high drop-out rates in modern trials on antipsychotic drugs (Wahlbeck et al. 2001), the LOCF approach underestimates the true weight gain risk so that completer analyses should be presented in addition. The access to weight data for all study visits also enabled us to use more time points for each patient in the regression analysis. A limitation of our approach was that we could not use data of studies that were not included in the database; but due to the relatively large number of patients included, the results should be rather robust.

In summary we conclude that amisulpride is an "atypical" antipsychotic associated with relatively little weight gain that is largely independent of dose.

References

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ (1999) Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 156:1686–1696

Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F (1995) Treatment of negative symptoms in schizophrenia with amisulpride. Br J Psychiatry 166:68–72

Brecher M, Rak IW, Melwin K, Jones AM (2000) The long-term effect of quetiapine (Seroquel^{TM}) monotherapy on weight in patients with schizophrenia. Int J Psych Clin Pract 4:287–291

Bressan RA, Erlandsson K, Jones HM, Mulligan R, Flanagan RJ, Ell PJ, Pilowsky LS (2003) Is regionally selective D_2/D_3 dopamine occupancy sufficient for atypical antipsychotic effect? An in vivo quantitative (^{123}I) epidepride SPET study of amisulpride-treated patients. Am J Psychiatry 160:1413–1420

Carrière P, Lempérière T, Bonhomme D (2000) Amisulpride study group: amisulpride has a superior benefit:risk profile to haloperidol in schizophrenia: results of a multicentre, double-blind study. Eur Psychiatry 15:321–329

Colonna L, Saleem P, Dondey-Nouvel L, Rein W (2000) Amisulpride study group: long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. Int Clin Psychopharmacol 15:13–22

Costa e Silva JA (1989) Comparative double-blind study of amisulpride versus haloperidol in the treatment of acute psychotic states. In: Amisulpride. Expansion scientifique francaise, Paris, pp 93–104

Danion JM, Rein W, Fleurot O (1999) Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Am J Psychiatry 156:610–616

Delcker A, Schoon ML, Oczkowski B, Gaertner HJ (1990) Amisulpride versus haloperidol in treatment of schizophrenic patients—results of a double-blind study. Pharmacopsychiatry 23:125–130

Jody D, Saha AR, Iwamoto T, Biswas D, Lin C, Marcus R, McQuade RD (2002) Meta-analysis of weight effects with aripiprazole. Int J Neuropsychopharmacol 5:S186

Klein HE, Dieterle D, Rüther E, Eben E, Nedopil N, Hippius H (1985) A double-blind comparison of amisulpride vs. haloperidol in acute schizophrenic patients. In: Pichot P, Berner P, Wolf R, Thau K (eds) Psychiatry, "The state of the art". Plenum Press, Cambridge Mass., pp 687–691

Leucht S, Pitschel-Walz G, Engel R, Kissling W (2002) Amisulpride—an unusual atypical antipsychotic. A meta-analysis of randomized controlled trials. Am J Psychiatry 159:180–190

Loo H, Poirier-Littre MF, Theron M, Rein W, Fleurot O (1997) Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. Br J Psychiatry 170:18–22

Möller HJ, Boyer P, Fleurot O, Rein W (1997) Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison with haloperidol. Psychopharmacology 132:396–401

Mota Neto JNE, Lima MS, Soares BO (2002) Amisulpride for schizophrenia (Cochrane Review). In: The Cochrane Library. Update Software, Oxford

NICE—National Institute for Clinical Excellence (2002). Guidance on the use of newer (atypical) drugs. Technology appraisal guidance No 43. www.nice.org.uk

Paillère-Martinot ML, Lecrubier Y, Martinot JL, Aubin F (1995) Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. Am J Psychiatry 152:130–134

Perrault GH, Depoortere R, Morel E, Sanger DJ, Scatton B (1997). Psychopharmacological profile of amisulpride: an antipsychotic drug with presynaptic D2/D3 dopamine receptor antagonist acitivity and limbic selectivity. J Pharmacol Exp Ther 280:72–83

Peuskens J, Bech P, Möller HJ, Bale R, Fleurot O, Rein W (1999) Amisulpride study group: amisulpride vs. risperidone in the treatment of acute exacerbations of schizophrenia. Psychiatry Res 88:107–117

Pichot P, Boyer P (1988) Etude multicentrique contrôlée en double insu: amisulpride (Solian 200) versus halopéridol à forte dose dans les états psychotiques aigus. Ann Psychiatr 3:326–332

Pichot P, Boyer P (1989) Controlled double-blind multi-centre trial of low dose amisulpride versus fluphenazine in the treatment of the negative syndrome of chronic schizophrenia. In: Amisulpride. Expansion scientifique francaise, Paris, pp 125–137

Puech A, Fleurot O, Rein W (1998) Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. Acta Psychiatr Scand 98:65–72

Rak IW, Jones AM, Raniwalla J, Phung D, Melvin K (2000) Weight changes in patients treated with Seroquel (quetiapine). Schizophr Res 41:206

Reynolds GP (1997) What is an atypical antipsychotic. J Psychopharmacol 11:195–199

Rüther E, Blanke J (1988) Therapievergleich von Aminosultoprid (DAN 2163) und Perazin bei schizophrenen Patienten. In: Helmchen H, Hippius H, Tölle R (eds) Therapie mit Neuroleptika—Perazin. Thieme Verlag, Stuttgart, pp 65–71

Saletu B, Küfferle B, Gruenberger J, Földes P, Topitz A, Anderer P (1994) Clinical, EEG Mapping and psychometric studies in negative schizophrenia: comparative trials with amisulpride and fluphenazine. Pharmacopsychiatry 29:125–135

Scatton B, Claustre Y, Cudenned A, Oblin A, Perrault G, Sanger DJ, Schoemaker H (1997) Amisulpride: from animal pharmacology to therapeutic action. Int Clin Psychopharmacol 12:S29–S36

Schoemaker H, Claustre Y, Fage D, Rouquier L, Chergui K, Curet O, Oblin A, Gonon F, Carter C, Benavides J, Scatton B (1997) Neurochemical characteristics of amisulpride, an atypical dopamine D_2/D_3 receptor antagonist with both presynaptic and limbic selectivity. J Pharmacol Exp Ther 280:83–97

Sèchter D, Peuskens J, Fleurot O, Rein W, Lecrubier Y (2002) Amisulpride study group: amisulpride vs. risperidone in chronic schizophrenia: results of a 6- month double-blind study. Neuropsychopharmacology 27:1071–1081

Speller JC, Barnes TRE, Curson DA, Pantelis C, Alberts JL (1997) One-year, low-dose neuroleptic study of in-patients with chronic schizophrenia characterised by persistent negative symptoms—amisulpride v. haloperidol. Br J Psychiatry 171:564–568

Taylor DM, McAskill R (2000) Atypical antipsychotics and weight gain—a systematic review. Acta Psychiatr Scand 101:416–432

Wahlbeck K, Tuunainen A, Ahokas A, Leucht S (2001) Drop-out rates in randomised antipsychotic drug trials. Psychopharmacology 155:230–233

Wetzel H, Grunder G, Hillert A, Philipp M, Gattaz WF, Sauer H, Adler G, Schroder J, Rein W, Benkert O (1998) Amisulpride versus flupentixol in schizophrenia with predominantly positive symptomatology—a double-blind controlled study comparing a selective D-2-like antagonist to a mixed D-1-/D- 2-like antagonist. Psychopharmacology 137:223–232

Ziegler B (1989) Study of the efficacy of a substituted benzamide amisulpride, versus haloperidol, in productive schizophrenia. In: Amisulpride. Expansion scientifique francaise, Paris, pp 73–81