Early-Onset Hypothesis of Antipsychotic Drug Action: A Hypothesis Tested, Confirmed and Extended

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Background: *A recent meta-analysis rejected the "delayed onset of antipsychotic action hypothesis" that had been described in textbooks for decades. Since meta-analyses are prone to a number of methodological problems, we attempted a replication by a) using a large database of individual patient data rather than meta-analysis, b) including another antipsychotic and c) extending the analysis from four weeks to one year.*

Methods: *We pooled the data of seven randomized trials involving amisulpride. The data included 1708 patients with schizophrenia and positive symptoms and we examined the incremental percentage Brief Psychiatric Rating Scale (BPRS) reduction over time.*

Results: *The "early onset of antipsychotic action hypothesis" was confirmed, as the reduction of overall and positive symptoms until week two was larger than the additional reduction until week four (p < .0001). Furthermore, in a subset with long-term data (n = 748) approximately 68% of the mean BPRS change at one year was already achieved at four weeks in the observed cases.*

Conclusions: *A substantial amount of the antipsychotic drug effect seems to occur during the first weeks of treatment. Subsequent analyses are needed to establish how long an antipsychotic should be tried before it is considered ineffective and alternative strategies implemented.*

It had been stated in textbooks for decades that there is a delay of onset of the action of antipsychotic drugs against the positive signs and symptoms of schizophrenia. This dogma was recently rejected by a meta-analysis by Agid et al (2003), who showed that a larger reduction of symptoms occurs during the first two weeks than during the second two weeks of treatment. Because of the major clinical and scientific implications of this publication, but also due to the well-known methodological limitations of meta-analyses (such as the need to make estimations when results are presented only in figures, the use of different rating scales in the trials or the difficulties in handling drop-outs in the calculations) we felt that a replication using a different approach and a different antipsychotic would be useful. In addition, Agid and colleagues (2003) restricted their analysis to four weeks of treatment, so that the further course of the antipsychotic effect remained unexamined. We therefore attempted to replicate their findings by a) analyzing a large database of individual patient data rather than using meta-analytic techniques, b) including another antipsychotic with a distinct receptor binding profile (amisulpride) which was not examined by Agid et al (2003) and c) extending the analysis to one year of treatment.

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Methods and Materials

The Database

We requested original patient data from seven randomized and double-blind studies (with one exception - Colonna et al 2000) on the efficacy of amisulpride in acutely ill patients with schizophrenia or schizophreniform disorder according to DSM-III-R or DSM-IV and pooled them for a post-hoc analysis (see Table 1). This represented the manufacturer's complete database of randomized controlled amisulpride trials in patients with schizophrenia and positive symptoms with the exception of one recent study that was not available when the project was begun (Mortimer et al 2004). Studies on patients with predominantly negative symptoms were explicitly excluded (Danion et al 1999; Loo et al 1997; Boyer et al 1995; Paillère-Martinot et al 1995; Speller et al 1997; Pichot and Boyer 1989; Saletu et al 1994). The latter studies assessed patients with predominently negative symptoms and usually only low levels of positive symptoms (according to various criteria); and with one exception (Speller et al 1997), all excluded paranoid schizophrenia. Data from these studies were not considered because the time course of the antipsychotic effect in patients with predominantly negative symptoms may be different, while we were interested in the effects on patients with pronounced positive symptoms. A summary of the characteristics of the latter studies (and of some very small old studies on positive symptom patients for which original patient data are not available any more due to the change of ownership of amisulpride – Klein et al 1985; Rüther and Blanke 1988; Pichot and Boyer 1988; Ziegler 1989; Costa e Silva 1989; Delcker et al 1990) has been presented in Leucht et al (2002). According to our experience with meta-analyses, authors are very hesitant to share original patient data, so that we did not attempt to include studies outside the manufacturer's database. However, a search in the register of the Cochrane Schizophrenia Group (August 2003) and regular MEDLINE searches up to December 2004 revealed no further relevant randomized controlled amisulpride trials.

As described in Table 1, two studies used a fixed-dose design (Puech et al 1998; Peuskens et al 1999) and two further studies also used a fixed-dose design but allowed one dose reduction from the initial dose to a lower one (Möller et al 1997, Wetzel et al 1998). In these trials the full doses of study drugs were already

Table 1. Characteristics of the Included Studies

Study	Antipsychotic Drugs and Daily Dose (mg)	*n*	Weeks	Selected Eligibility Criteria
Möller et al 1997	AMI 800/600[a] HAL 20/15[a]	95 96	6	Inpatients with paranoid, disorganized or undifferentiated schizophrenia. BPRS psychotic subscore ≥ 12 and at least 2 psychotic items ≥ 4
Wetzel et al 1998	AMI 1000/600[a] FLU 25/15[a]	70 62	6	Acutely admitted inpatients with paranoid or undifferentiated schizophrenia. BPRS total score ≥ 36, but no predominant negative symptoms defined as SANS composite score > 55
Puech et al 1998	AMI (100[b]; 400; 800; 1200) HAL 16	(61; 64; 65; 65) 64	4	Inpatients with acute exacerbations of paranoid, disorganized or undifferentiated schizophrenia. BPRS psychotic subscore subscore ≥ 12 and at least 2 psychotic items ≥ 4
Colonna et al 2000	AMI 200–800 HAL 5–20	370 118	51	Inpatients or outpatients with acute exacerbations of paranoid, disorganized or undifferentiated schizophrenia. BPRS psychotic subscore ≥ 12 and at least 2 psychotic items ≥ 4
Carrière et al 2000	AMI 400–1200 HAL 10–30	94 105	17	Inpatients with paranoid schizophrenia or schizophreniform disorder
Peuskens et al 1999	AMI 800 RIS 8	115 113	8	Inpatients or outpatients with paranoid, disorganized or undifferentiated schizophrenia. BPRS total score ≥ 36, BPRS psychotic subscore ≥ 12 and at least 2 psychotic items ≥ 4
Sèchter et al 2002	AMI 400–1000 RIS 4–10	152 158	51[c]	Inpatients or outpatients with schizophrenia. PANSS total score 60–120, no predominant negative symptoms defined as 3 or more PANSS negative items ≥ 4

AMI, amisulpride; HAL, haloperidol; FLU, flupentixol; RIS, risperidone; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the assessment of negative symptoms; PANSS, Positive and Negative Syndrome Scale.

[a]All patients were started at the higher dose, which could then be reduced.

[b]This potentially subtherapeutic dose group was excluded.

[c]In the original report only the results at 6 months were reported, but there was a double-blind extension to a total of 12-months that we used for our analysis.

given the first day without titration, with the exception of risperidone in Peuskens et al (1999), which was increased over a period of 4 days. In the three studies with a flexible-dose design (Colonna et al 2000; Carrière et al 2000; Sèchter et al 2002) doses could be adjusted whenever necessary within the specified ranges. However, in Carrière et al (2000) the doses at the first day were predefined to be 800 mg amisulpride and 20 mg haloperidol; and in Sèchter et al (2002) the amisulpride and risperidone doses were 600 mg/day and 6 mg/day (increased during 3 days) in the first week before adjustments were allowed.

The database initially contained 1867 patients. Sixty-one patients of one fixed-dose study (Puech et al 1998) who had received a potentially subtherapeutic dose of 100 mg/day amisulpride were excluded from all (primary and post-hoc sensitivity) analyses. To assure that the patients had positive symptoms at baseline (i.e. after the wash-out phases), only patients with at least two BPRS psychosis items (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content) rated moderate or higher and a total score of at least 12 on the combined 4 psychosis items were included in the analysis. This maneuver appeared warranted to make sure that the patients really had positive symptoms at baseline, because—although with two exceptions (Carrière et al 2000; Wetzel et al 1998) all studies required a minimum severity of positive symptoms in order to be eligible for the trials—eligibility was assessed prior to the wash-out phases so that at the time of randomization after the wash-out phases some patients no longer met this criterion. Only 98 of an initial total of 1867 patients were excluded on this basis,

so that the results were not affected to any important extent (see first sensitivity analysis). After these exclusions the database consisted of 1708 patients treated with amisulpride (*n* = 1042), haloperidol (*n* = 367), flupentixol (*n* = 47) or risperidone (*n* = 252). The mean BPRS at baseline was 58.6 ± 14.5, the mean psychotic subscore 18.1 ± 3.2, the mean age 36.0 ± 10.9 years, the mean duration of illness 10.4 ± 8.6 years (for 116 patients this information was not recorded), the mean weight 70.6 ± 14.5 kg; there were 1054 men and 654 women, 1671 had schizophrenia and 37 had schizophreniform disorder. At baseline 1136 participants were inpatients, 156 were outpatients, 157 were being treated in day hospitals, and for 259 participants the treatment setting was not recorded.

Data Analysis

The percentage BPRS reduction (B%) at each week was calculated using the formula B% = $(B_0 - B_i) * 100 / (B_0 - X)$, where B_0 = BPRS at baseline, B_i = BPRS at week i, and X is the minimum score of the BPRS in the 1 to 7 rating system (18 for the total score and 4 for the psychotic subscore). Since all studies presented data on the BPRS in contrast to the analysis of Agid and colleagues, which combined BPRS derived and PANSS derived data, standardization for the use of different scales was not necessary. The weekly percentage reduction was calculated for the total score and the psychotic items subscore (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content). Instead of an estimation using a regression model as in Agid et al's (2003) report, drop-outs could be