Depression in schizophrenia: Comparison of first- and second-generation antipsychotic drugs

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Abstract

The aim of this study was to compare the effects of different antipsychotics on depressive symptoms in schizophrenic patients. The data were drawn from a retrospective, naturalistic, observational study in which 222 subjects diagnosed as being affected by schizophrenia during a re-exacerbation phase received 6 weeks of monotherapy with fluphenazine decanoate, haloperidol decanoate, haloperidol, clozapine, olanzapine, quetiapine, risperidone or l-sulpiride. The Brief Psychiatric Rating Scale (BPRS), Extrapyramidal Side Effects Rating Scale (EPSE) and Anticholinergic Rating Scale (ACS) were administered at baseline and six weeks after the beginning of the study; depressive symptoms were evaluated using the BPRS items “depressive mood” and “guilt feelings”.

All of the antipsychotic drugs led to improvements in the depressive dimension, but this was statistically significant only in the case of fluphenazine decanoate, haloperidol, olanzapine, risperidone and l-sulpiride. A clinical improvement in the depressive dimension significantly correlated with the severity of the psychotic picture and its amelioration. Female patients were significantly more likely to show an improvement in depressive symptoms.

In conclusion, our findings suggest that atypical antipsychotics as a class do not seem to be more effective on the depressive dimension during the course of schizophrenia than typical ones, at least as far as the collected BPRS data are concerned. The only factor that seemed to influence the improvement in depressive symptoms during our study was gender, as females were significantly more likely to improve although there were no between-gender differences in the baseline severity of the clinical picture.

Keywords: Schizophrenia; Depressive symptoms; Antipsychotics; Female gender

1. Introduction

It is generally acknowledged that depressive symptoms represent an important and distinct symptom domain in schizophrenia (Siris et al., 2001), and may occur at any time during the course of the illness (Sands and Harrow, 1999; Siris and Bench, 2003). Most recent research has shown that they indicate a poor prognosis in terms of recovery and reintegration into the community (Resnick et al., 2004), and they clearly play a part in the devastating long-term nature of schizophrenia. Mood state, energy loss, impaired concentration and reduced self-confidence are depressive dimensions that
materially contribute to the loss of social and vocational capacity experienced by schizophrenic subjects (Siris and Bench, 2003), thus reducing their quality of life (Norholm and Bech, 2006). In other words, people with schizophrenia and concurrent depressive symptoms are significantly more likely than non-depressed schizophrenic patients to use relapse-related mental health services, to be a safety concern, to have greater substance-related problems, and to report poorer life satisfaction, quality of life, mental functioning, family relationships and medical adherence (Conley et al., 2007). The importance and severity of depression in schizophrenia is sustained by the high 10–15% rate of suicide, which is the leading cause of premature death among schizophrenics (Roy, 1990; Hunt et al., 2006).

It has been reported that the prevalence of depressive symptoms during the course of schizophrenia ranges from 25% to 80% (DeLisi, 1990; Mauri et al., 1995; Mauri et al., 1999), depending on the phase of the illness, patient age (Zisook et al., 2006), treatment setting, and the definition of depression (Hausmann and Fleischhacker, 2002).

Some authors suggest that depressive symptoms may be related to schizophrenia when the full-blown psychosis is most evident (so-called “revealed depression”) (Hirsh et al., 1990), thus suggesting that the depression may be associated with the psychotic state itself or a subjective reaction to the experience of psychotic decompensation. Furthermore, it has classically been reported that depressive symptoms are induced by neuroleptic therapy in 15–50% of patients (“pharmacogenic depression”) (Kapur and Mann, 1992; Bressan et al., 2002), and that “akinetic depression” may be considered a variant of pharmacogenic depression and related to the akinetic syndromes induced by neuroleptics (Van Putten and May, 1978).

Therefore it would be useful to measure neuroleptic side effects, in order to determine if any observed antidepressant action might be a confound of the difference in side effects.

Therapeutic interventions aimed at treating depressive symptoms in schizophrenic patients help to improve individual patients’ quality of life and compliance with therapeutic projects. In a number of cases, the choice of an antipsychotic medication may also depend on its “antidepressant” efficacy.

The aim of this study was to compare the effects of different antipsychotics on depressive symptomatology in schizophrenic patients. In particular we compared the effects of three typical antipsychotics (fluphenazine decanoate (FLZ-D), haloperidol decanoate (HL-D) and haloperidol (HL)), and five atypical agents (clozapine (CLZ), olanzapine (OLZ), quetiapine (QTP), risperidone (RSP) and l-sulpiride (L-SLP) in a naturalistic setting.

2. Materials and methods

The data were drawn from a retrospective, naturalistic, observational study of 222 subjects (167 males and 55 females) diagnosed as being affected by schizophrenia on the basis of the DSM IV criteria, and admitted to the Psychiatry Clinic of Milan’s Ospedale Maggiore Policlinico during a re-exacerbation phase. The patients fell into eight groups, and each received 6 weeks of monotherapy with CLZ (n=19), FLZ-D (n=44), HL-D (n=26), HL (n=26), OLZ (n=54), QTP (n=19), RSP (n=19) or L-SLP (n=15); the treatment was chosen by the individual clinicians on the basis of the clinical picture. The mean administered doses at baseline (T0) were CLZ 304.89 mg/day (111.65 SD), FLZ-D 22.23 mg/day (6.17 SD), HL-D 11.3 mg/day (5.97 SD), HL 9.68 mg/day (3.93 SD), OLZ 14.95 mg/day (5.60 SD), QTP 489.90 mg/day (186.91 SD), RSP 4.47 mg/day (1.12 SD), L-SLP 279.8 mg/day (44.61 SD). The only other drugs allowed during the study were benzodiazepines in the case of dire necessity.

The protocol was approved by our local Ethics Committee, and the patients or their relatives were asked to consent to having their data accessed for future use at the time they were admitted.

The Brief Psychiatric Rating Scale (BPRS,1988) and Extrapyramidal Side Effects Rating Scale (EPSE,1970) were administered at baseline (T0) and six weeks after the beginning of the treatment (T1). Anti-cholinergic side effects were evaluated on the basis of a check list (ACS) (Altamura et al., 1987). Extrapyramidal side effects were evaluated as: 0–3 = absence of symptom (Simpson and Angus, 1970), 4–10 = mild, 11–18 = moderate and 19–35 = severe. All rating scales were administered by raters who were blinded to the aim of the study; the investigators were trained in the use of the rating scales before the start of the study in order to ensure inter-rater consistency.

Depressive symptoms were evaluated using the BPRS items “depressive mood” and “guilt feelings” of the Depression Factor (Overall and Gorham, 1988; Hausmann and Fleischhacker, 2002; Velligan et al., 2005); each item was scored from 0 to 7 on the basis of the BPRS Rating Scale, and the scores for the two items were averaged in order to obtain a single mean value for each patient. Values of 0–1.9 = no depression; 2–3.9 = mild; 4–5.9 moderate; and 6–7 = severe.

Motor retardation, sedation, was considered a separate item (0–1 = absence of symptom; 2–3 =
mild; 4–5 = moderate; 6–7 = severe) given its clear link to drug-induced extrapyramidal symptoms, at least in the case of typical antipsychotics (Van Putten and May, 1978; Hausmann and Fleischhacker, 2002).

The data were analysed by means of descriptive statistics, analysis of variance (ANOVA), multifactor analysis of variance (Tukey’s test), regression analysis and multivariate testing (logistic regression) using Statgraphics 5 Plus Windows software (Statistical Graphics Corporation, 2000).

3. Results

Table 1 shows the patients’ characteristics.

All of the patients showed a clinically significant improvement in the total BPRS score at the end of the study: the improvements were 23.19% (±22.99% SD) for CLZ, 32.73% (±27.98% SD) for FLZ-D, 28.59% (±20.73% SD) for HL-D, 37.43% (±16.13% SD) for HL (p < 0.01 vs OLZ and QTP), 20.27% (±17.97% SD) for OLZ, 18.19% (±24.26% SD) for QTP, 30.83% (±11.91% SD) for RSP and 31.87% (±12.94% SD) for L-SLP.

At baseline, 48.99% of the patients were mildly depressed, 13.77% moderately depressed, and 0.81% seriously depressed as assessed on the basis of the BPRS items “depressive mood” and “guilt feelings”; at the end of the study, 40.60% were mildly depressed, 5.98% moderately depressed, and none showed severe depression. All of the antipsychotic agents improved the depressive dimension, but the improvement was statistically significant only in the case of FLZ-D, HL, OLZ, RSP and L-SLP (p < 0.05). None of the drugs seemed to have a real depressogenic effect (Table 2).

There was no correlation between the severity of the depressive symptoms and the doses of the antipsychotics. There was a significant (p < 0.001) positive correlation between the improvement in the BPRS depressive

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>CLZ</th>
<th>FLF-D</th>
<th>HL-D</th>
<th>HL</th>
<th>OLZ</th>
<th>QTP</th>
<th>RSP</th>
<th>L-SLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
<td>M F</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>36.42(7.30)</td>
<td>43.9(16.39)</td>
<td>31.46(8.26)</td>
<td>32.39(13.01)</td>
<td>35.65(12.36)</td>
<td>38.95(14.95)</td>
<td>36.94±10.30</td>
<td>46.66±17.79</td>
</tr>
<tr>
<td>Mean age of Onset, years(SD)</td>
<td>22.84(4.87)</td>
<td>26.92(6.04)</td>
<td>23.24(6.27)</td>
<td>24.53(10.36)</td>
<td>27.34(9.91)</td>
<td>28.47(12.88)</td>
<td>20.55(2.0)</td>
<td>27.06(9.98)</td>
</tr>
<tr>
<td>Dur. of illness, mean(SD)</td>
<td>13.57(7.35)</td>
<td>14.53(13.39)</td>
<td>8.76(5.94)</td>
<td>7.92(8.27)</td>
<td>6.90(6.27)</td>
<td>10.94(12.39)</td>
<td>16.55(10.36)</td>
<td>19.16(19.5)</td>
</tr>
</tbody>
</table>

Diagnosis

<table>
<thead>
<tr>
<th>S. Cat</th>
<th>S. Dis</th>
<th>S. Und</th>
<th>S. Par</th>
<th>S. Res</th>
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</thead>
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<tr>
<td>0%</td>
<td>26.32%</td>
<td>47.37%</td>
<td>26.32%</td>
<td>0%</td>
</tr>
<tr>
<td>0%</td>
<td>31.82%</td>
<td>43.18%</td>
<td>22.73%</td>
<td>0%</td>
</tr>
<tr>
<td>0%</td>
<td>38.46%</td>
<td>30.77%</td>
<td>30.77%</td>
<td>0%</td>
</tr>
<tr>
<td>0%</td>
<td>23.73%</td>
<td>59.32%</td>
<td>16.95%</td>
<td>7.41%</td>
</tr>
</tbody>
</table>

BPRS T0, mean(SD)**

| BPRS T0, mean(SD)** | 51.10(14.56) | 69.00(14.00) | 50.30(11.35) | 56.45(11.56) | 51.64(11.03) | 52.42(7.55) |

BPRS T1, mean (SD)

| BPRS T1, mean (SD) | 36.79(9.87) | 45.71(20.24) | 34.48(6.74) | 34.21(8.66) | 40.06(9.94) | 41.62(10.00) | 40.37(12.81) | 35.18(8.54) |

Motor retardation T0, mean (SD)

| Motor retardation T0, mean (SD) | 2.16(1.34) | 3.88(1.74) | 2.27(1.91) | 2.85(1.86) | 1.98(1.22) | 2.05(1.75) | 3.84(1.74) | 3.92(1.73) |

Motor retardation T1, mean (SD)#

| Motor retardation T1, mean (SD)# | 2.11(1.15) | 3.2(1.99) | 1.73(1.15) | 2.16(1.45) | 1.69(0.99) | 1.75(1.24) | 2.95(1.43) | 2.27(0.79) |

EPSE T0, mean (SD)

| EPSE T0, mean (SD) | 2.63(6.3) | 3.98(6.13) | 1.53(2.59) | 3.37(5.04) | 1.06(3.28) | 2.26(5.30) | 5.65(8.19) | 5.17(5.64) |

EPSE T1, mean (SD)

| EPSE T1, mean (SD) | 2.04(3.3) | 11.12(9.67) | 2.67(2.69) | 3.69(3.87) | 0.39(2.11) | 2.19(5.08) | 1.42(3.41) | 2.67(3.32) |

ACS T0, mean (SD)

| ACS T0, mean (SD) | 0.47(0.91) | 0.83(1.64) | 0.89(1.59) | 1.28(1.78) | 0.23(0.66) | 0.42(1.00) | 1.06(2.11) | 1.67(1.97) |

ACS T1, mean (SD)

| ACS T1, mean (SD) | 0.74(0.99) | 1.55(1.83) | 0.67(0.89) | 0.74(1.09) | 0.15(0.63) | 0.08(0.28) | 0.05(0.23) | 0.56(0.73) |

Dose in mg

| Dose in mg | 304.89(111.655) | 22.23(6.77) | 11.35(5.97) | 9.68(5.93) | 14.95(5.60) | 489.90(186.91) | 44.7(1.12) | 279.8(44.61) |

Abbreviation: SD, standard deviation; CLZ, Clozapine; FLF-D, Fluphenazine Decanoate; HL-D, Haloperidol Decanoate; HL, Haloperidol; OLZ, Olanzapine; RSP, Risperidone; L-SLP, L-Sulpiride.

S.Cat, Catatonic Schizophrenia; S.Dis, Disorganized Schizophrenia; S.Und, Undifferentiated Schizophrenia; S.Par, Paranoid Schizophrenia; S.Res, Residual Schizophrenia.

*p < 0.001 for FLF-D vs HL-D, HL, OLZ and for L-SLP vs HL-D and HL.

**p < 0.001 for FLF-D vs HL and OLZ and for L-SLP vs HL-D, HL and OLZ.

***p < 0.001 for FLF-D vs all the other drugs.

#p < 0.001 for FLF-D vs HL-D, HL, OLZ and QTP.
items and the baseline total BPRS score (excluding the two depressive items), and also a significant ($p < 0.001$) positive correlation between the improvement in the BPRS depressive items and the improvement in the total BPRS score.

The patients treated with FLZ-D had the highest motor retardation score (mean $3.2 \pm 1.98$ SD; $p < 0.001$ vs HL-D, HL, OLZ, QTP) while OLZ showed the lowest motor retardation scores (Table 1).

FLZ-D showed at the end of the study the highest percentage of patients with moderate and severe EMSE scores (42.86%); HL showed a percentage of patients with moderate scores of 7.69%. OLZ showed the highest percentage of patients without extrapyramidal side effects (98.04%).

There was no significant correlation between depressive symptoms and the EPSE or ACS score, but there was a significant correlation between the EPSE score and motor retardation (Fig. 1).

Multivariate testing of the variables age, gender, duration of illness, dose at T1, and typical/atypical antipsychotic showed that female patients were significantly more likely to show an improvement in depressive symptoms: i.e. an improvement of $\geq 20\%$ on the two BPRS items (Table 3).

### Table 2

Mean score of BPRS items “depressive mood” and “guilt feelings” for each patient group (BPRS DEP) before (T0) and after (T1) each of the eight neuroleptic treatments ($p < 0.05$)

<table>
<thead>
<tr>
<th>Drug</th>
<th>BPRS DEP mean values (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
</tr>
<tr>
<td>CLZ</td>
<td>3.68 (1.89)</td>
</tr>
<tr>
<td>FLZ-D*</td>
<td>6.15 (2.60)</td>
</tr>
<tr>
<td>HL-D</td>
<td>3.77 (2.42)</td>
</tr>
<tr>
<td>HL*</td>
<td>4.26 (2.36)</td>
</tr>
<tr>
<td>OLZ*</td>
<td>5.09 (2.56)</td>
</tr>
<tr>
<td>QTP</td>
<td>3.26 (1.91)</td>
</tr>
<tr>
<td>RSP*</td>
<td>5.68 (2.08)</td>
</tr>
<tr>
<td>SLP</td>
<td>5.17 (1.99)</td>
</tr>
</tbody>
</table>

* $p < 0.05$ (T1 vs T0).

### Table 3

Multivariate testing of the variables age, gender, duration of illness, dose at T1 and typical/atypical antipsychotics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
<th>Estimated odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>$-0.41$</td>
<td>$0.74$</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>$0.04$</td>
<td>$0.02$</td>
<td>$1.04$</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>$-0.05$</td>
<td>$0.03$</td>
<td>$0.95$</td>
</tr>
<tr>
<td>Dose</td>
<td>$0$</td>
<td>$0$</td>
<td>$1$</td>
</tr>
<tr>
<td>Gender</td>
<td>$-0.93$</td>
<td>$0.36$</td>
<td>$0.39$</td>
</tr>
<tr>
<td>Typical/atypical</td>
<td>$0.06$</td>
<td>$0.38$</td>
<td>$1.07$</td>
</tr>
</tbody>
</table>

Likelihood ratio test

<table>
<thead>
<tr>
<th>Factor</th>
<th>Chi-square</th>
<th>$df$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.46</td>
<td>1</td>
<td>0.12</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>2.82</td>
<td>1</td>
<td>0.09</td>
</tr>
<tr>
<td>Dose</td>
<td>1.08</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Gender</td>
<td>6.92</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Typical/atypical</td>
<td>0.03</td>
<td>1</td>
<td>0.87</td>
</tr>
</tbody>
</table>

The only factor that seems to predict the improvement in depressive symptoms is gender.

4. Discussion

We found a frequency of depression in chronic schizophrenic patients during a period of symptom exacerbation in line with the published data: $63.57\%$ of our patients had depressive symptoms at baseline, and $46.58\%$ after 6 weeks of monotherapy (DeLisi, 1990; Mauri et al., 1995; Conley et al., 2007; Häfner et al., 2005) during which all of them showed a general clinical improvement as measured by BPRS (28.77%).

Like previous authors (Häfner et al., 2005), we found that a clinical improvement in the depressive dimension significantly correlated with the severity of the psychotic picture and its improvement, in line with the concept of “revealed depression”.

All of the typical and atypical antipsychotics alone improved depressive symptoms evaluated as a cluster, but this improvement was statistically significant only in the case of FLZ-D, HL, OLZ, RSP and L-SLP, which partially conflicts with some published data concerning the depressogenic effect of classical neuroleptics (“pharmacogenic depression”), especially FLZ-D and HL (Ayd, 1978; Rifkin, 1981; Johnson, 1985; Krakowsky...
et al., 1997). On the other hand, some experimental data suggest that HL has a disinhibitory effect on emotion, particularly at low doses (Pich and Samanin, 1986), and not all studies support a depressogenic effect of FLF-D which, despite being a depot neuroleptic, has a rapid clinical effect due to its particular pharmacokinetic profile (Altamura et al., 1987).

It seems to be more difficult to explain the effect of HL-D on the depressive items of the BPRS, but it should be remembered that the patients were in an acute phase; furthermore, the fact that HL-D improved depression to a lesser extent may have been due to the short duration of the study insofar as the pharmacokinetic characteristics of the drug mean that it takes about four months to reach steady-state plasma levels.

The results were clearer in the case of L-SLP, which has molecular affinity with amisulpride, and confirmed its previously described disinhibitory effect on emotion and activating properties, particularly at low and intermediate doses (the mean dose in our study was 280 mg/day) (Lecrubier et al., 2006).

The poor effect of CLZ on depressive dimension may also be due to the greater personal insight it induces as recent studies have confirmed that there is a close correlation between depressive symptoms and disease awareness (Bourgeois et al., 2004). On the other hand, it has also been reported that the drug has anti-suicide properties (Spivak et al., 2003; Meltzer et al., 2003), although it is known that suicidality in schizophrenic patients is not only related to depression, but also to various other psychopathological aspects (Hunt et al., 2006) such as hallucinatory phenomena inducing patients to commit self-aggressive behaviours, and the absence of affective sensitivity and lack of control over aggression may contribute to determining the risk of suicide. Such psychopathological correlates may be better controlled by CLZ than other molecules (Spivak et al., 1997).

The results obtained with OLZ and RSP fit their pharmacodynamic effects on dopaminergic and serotonergic systems (Marder et al., 1997; Mauri et al., 2005; Lecrubier et al., 2006) and clinical data in the treatment of patients with affective symptomatology. (Jarema, 2007).

As found in previous studies (Emsley et al., 2003), QTP improved depressive symptoms but not in a statistically significant manner probably because of the prevalence of paranoid schizophrenia, traditionally considered to be less drug responsive (van Kamentschidem and Schooler, 1990).

There was no relationship between the EPSE and ACS and the antidepressant effect of the drugs: in other words, extrapyramidal and anticholinergic side effects did not seem to influence the depressive status of patients at the end of the study.

However, extrapyramidal symptoms were clearly related to the BPRS “motor retardation” item, a symptom that characterises depression but is not suitable for evaluating depression in schizophrenia treated with (particularly typical) antipsychotic drugs.

This study has a number of limitations, including the low level of depressive symptoms in some groups, the different number of patients treated with the various antipsychotics, and the different baseline depression scores obtained using the two BPRS depressive items (although the baseline scores were not significantly different in all groups.

In conclusion, atypical antipsychotics as a class per se do not seem to be more effective on the depressive dimension during the course of schizophrenia than their typical counterparts, and none of the typical antipsychotics seemed to exert a depressogenic effect. The only factor that seemed to affect the improvement in depressive symptoms was gender: females were significantly more likely to improve, although there were no between-gender differences in the baseline severity of the clinical picture.

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No funding source is present.

Contributors
All authors contributed to and have approved the final manuscript.

Conflicts of interest
None of the authors have any conflicts of interest.

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References


