SERTRALINE FOR THE PREVENTION OF RELAPSE IN DETOXICATED ALCOHOL-DEPENDENT PATIENTS WITH A COMORBID DEPRESSIVE DISORDER: A RANDOMIZED CONTROLLED TRIAL

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Abstract — Aims: We performed a double-blind, placebo-controlled randomized trial of sertraline in recently detoxified alcohol-dependent patients with current depressive symptoms. The objectives of the study were to evaluate the efficacy of sertraline at achieving stable abstinence, at ameliorating depressive symptoms and at improving quality of life in these patients. Methods: The study included 83 patients, who received either sertraline (50–150 mg/day) or placebo for 24 weeks. The primary outcome criteria were the rate of relapse into alcohol consumption and the rate of response on the Montgomery and Asberg Depression Rating Scale (MADRS). Results: At the end of the treatment period, relapse rates were 23.1% in the placebo group and 31.8% in the sertraline group. Responder rates for depression were 38.5% for the placebo group and 44.2% for the sertraline group. There was no significant difference between treatment groups with either variable. However, when patients were stratified into severe (MADRS score ≥26) and moderate (MADRS score <26) depression at inclusion, a significant treatment benefit with sertraline was observed in the former group. Quality of life, determined by the SF-36, improved in both groups, with more benefit observed for the sertraline group on mental health items. Sertraline was well tolerated, and the incidence of adverse events was similar in the two treatment groups. Conclusions: The explanation for the overall good outcome in both treatment groups and for the inability to demonstrate a clear treatment effect may reside in the clinical features of the patients included.

INTRODUCTION

Comorbidity of depression and alcohol dependence is common (Regier et al., 1990; Kessler et al., 1994); major depressive episodes appear to be approximately twice as frequent in alcohol-dependent patients than they are in the general population. Comorbid depression is a negative prognostic factor for achieving stable abstinence in alcohol dependence (Rounsaville et al., 1987; O’Sullivan et al., 1988; Driessen et al., 2001) whilst active alcohol dependence is a negative prognostic factor for remission of depressive symptoms (Mueller et al., 1994). In addition, comorbidity is associated with an increased risk of suicide (Murphy et al., 1992). For these reasons, identification and treatment of depressive symptoms is an important issue in the management of alcohol-dependent patients.

Understanding the origin and course of depression in alcohol-dependent patients has important implications for how it should be treated (O’Sullivan, 1984; Thase et al., 2001). Several different hypotheses have been put forward to account for this increased comorbidity (Berner et al., 1986; Swendsen and Merikangas, 2000). First, it is possible that depression and alcohol dependence exist as distinct pathologies in individuals who are predisposed to them as a result of common aetiological factors. These could be either genetic susceptibility factors (Kendler et al., 1997), or priming events occurring early in life such as childhood trauma (Roy, 1996a). Second, alcohol dependence and depression may be causally linked. Depressive symptoms may appear as a consequence of chronic alcohol use in subjects who had no history of depression prior to starting drinking. Alternatively, depression may precede and trigger excessive alcohol consumption as an ‘automedication’ response. These pathways to comorbidity are not mutually exclusive, and patient subgroups with different aetiologies may exist. For example, Schuckit (1983) postulated 20 years ago that patients could be divided into two groups, primary alcoholics with secondary depression, and symptomatic alcoholics with premorbid depression. The latter may correspond to the Type III alcoholics with chronic mood disorders described by Lesch (Lesch et al., 1988). The different hypotheses do, however, make a testable prediction, namely that if depression is secondary to alcohol dependence, it should resolve with abstinence, whereas if alcohol dependence is secondary to depression, or if the two are independent, then it should not resolve. Numerous studies (e.g. Brown and Schuckit, 1988; Brown et al., 1995; Kiefer and Barocka, 1999) have reported that depressive symptoms do indeed abate spontaneously within a month of detoxification in alcohol-dependent patients without premorbid depression, whilst they do not in those with symptomatic alcoholism. On the other hand, in patients with pre-existing depression, drinking behaviour may improve following successful treatment of depressive symptoms.

If depressive symptoms resolve spontaneously with abstinence, it may not be necessary specifically to treat depression once detoxification has been successfully completed, at least in primary alcoholism (Schuckit, 1985, 1994; Anthenelli and Schuckit, 1993). Treatment remains necessary in patients with symptomatic alcoholism. However, even in patients with primary alcoholism, antidepressant treatment may be useful in order to hasten the rate of recovery and thus decrease the risk of relapse or suicide. In addition, given the proposed role of serotonergic dysfunction in both depression and alcohol dependence (Heinz et al., 2001), antidepressants acting on this transmitter system may have additional beneficial effects on drinking behaviour. Data
showing that selective serotonin reuptake inhibitors (SSRI) consistently reduce alcohol consumption in experimental animals and from healthy human volunteers, have supported this notion (Sellers et al., 1991; Naranjo and Knoke, 2001).

There have been a number of clinical trials of antidepressants in alcohol dependence in patients with or without depressive symptoms, whose results have conflicted (Kranzler 2000; Thase et al., 2001). Most data suggest that SSRI and tricyclic antidepressants have limited, if any, efficacy on reducing consumption in non-depressed subjects, whereas in patients with pre-existing depression (symptomatic alcoholism) both depressive symptoms and drinking behaviour improved. However, differences in the study populations included, and in the methodology used, make comparisons and conclusions difficult. The most extensive data concern the use of fluoxetine and citalopram.

Four studies have evaluated the use of sertraline in depressed alcohol-dependent patients. A small first open-label uncontrolled study in 17 recently detoxified alcohol-dependent patients showed improvement of depressive symptoms (Roy, 1996b). This stimulated a double blind, placebo-controlled trial in the same centre (Roy, 1998), which demonstrated a more rapid resolution of depressive symptoms in patients treated with sertraline compared to placebo. All the patients were abstinent throughout the study. This was followed by a larger clinical trial in 100 patients, stratified according to the presence or absence of lifetime depression (Pettinati et al., 2001). In this study, depressive symptoms improved in both treatment groups of depressed patients, with no difference between groups. Patients were stratified according to lifetime incidence of depression. Drinking outcome was superior in the sertraline treatment set for patients without a history of depression, but not for patients with current or previous depression. In the fourth study, which was also randomized and placebo-controlled, 58 non-depressed, recently-detoxified alcohol-dependent patients were treated either with sertraline or with placebo for 6 months (Coskunol et al., 2002). A small and transient difference in abstinence rates between treatment groups in favour of sertraline was observed.

In light of the somewhat contradictory findings previously obtained, we have carried out a further double-blind, placebo-controlled randomized trial of sertraline in recently detoxified patients with current depressive symptoms. This study had two primary objectives: (1) to evaluate the efficacy of sertraline at achieving stable abstinence in recently detoxified alcohol-dependent patients with major depression or dysthymia, and (2) to evaluate the efficacy of this drug at ameliorating depressive symptoms and quality of life in these patients. A secondary objective was to evaluate the tolerability and safety of sertraline in such patients. Because patient heterogeneity may have contributed to the variability in the results of previous studies of SSRI in alcohol-dependent patients, strict entry criteria were imposed in order to increase the chances of obtaining an unambiguous result.

PATIENTS AND METHODS

The study was a double-blind, placebo-controlled, parallel group randomized clinical trial, performed in a single centre, the Alcohol Unit of the Hospital ‘Clínico y Provincial’ in Barcelona. The inclusion period lasted from February 1998 to January 2001, and the treatment period for 24 weeks following inclusion.

Patients

Patients were recruited into the study from those outpatients attending the Alcohol Unit therapeutic programme, and having recently undergone an acute alcohol detoxification.

In order to enter the study, patients were required to be at least 18 years old, to fulfill DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organisation, 1992) diagnostic criteria for alcohol dependence and for major depression or dysthymia or both, and to have remained abstinent for at least 2 weeks following detoxification. In addition, patients had to have a negative drug and alcohol urine screen at inclusion. Female patients of child-bearing age had to have a negative pregnancy test at inclusion, and were required to use an effective and safe contraceptive method for the 3 months preceding the study, and throughout the study duration. Written informed consent was required from all patients.

The following patients were excluded from the study. (1) Women who were pregnant, breast-feeding or who were of childbearing potential and were not using reliable contraceptive methods or who wished to become pregnant during the study or within a month after the study. (2) Patients with a primary psychiatric disorder apart from alcohol dependence and depressive symptoms. (3) Patients with moderate or severe liver disease including active cirrhosis or acute hepatitis. (4) Patients showing a high suicide risk. (5) Patients whom the investigator considered would require therapy with additional psychotropic drugs, electroconvulsive therapy (ECT) or intensive psychotherapy during the study. (6) Patients with a history of convulsive disorders, cerebral organic disease or laxative misuse within the 6 months prior to receiving the test drug. (7) Patients who had received therapy with depot neuroleptics during the 6 months prior to their inclusion in the study. (8) Patients requiring therapy with reserpine, methyldopa, guanetidine or clonidine, or who might require general anaesthesia or drugs that interact with sertraline or any serotonergic drug during the study. (9) Patients with a history of failure on sertraline or any other serotonin reuptake selective inhibitor, either alone or combined with another therapy, for treating the current depressive episode. (10) Patients in whom sertraline therapy was contraindicated. (11) Patients with the following diseases: severe allergies or multiple adverse reactions to drugs, unstable thyroid disease, severe organic diseases, or patients who had suffered severe infections or major surgery one month before their inclusion in the study. (12) Patients considered being insufficiently motivated for the therapy or with other emotional or intellectual problems that might limit the patient’s ability to comply with the protocol requirements. (13) Patients who had been involved in other clinical studies within the 6 months prior to the onset of this study or who were involved in such studies simultaneously with this study. (14) Patients who had not undergone a sufficient wash-out period since the administration of previous psychotropic medication. (15) Patients who insisted on giving blood while participating in the study and/or a month after the...
end of the study. (16) Patients with a prothrombin time out of normal range.

Patients fulfilling the entry criteria were then randomized to receive either placebo or sertraline (50–150 mg/day) for the following 24 weeks. The investigator did not have access to the randomization code. The sertraline dose was initially 50 mg/day and could be titrated up to 150 mg/day over the first 8 weeks at the investigator’s discretion. Matching packets containing placebo were provided for all possible sertraline dose progressions, so that titration could be performed double-blind. Patients were issued with diary cards on which to record alcohol consumption on a daily basis. Study visits were programmed at 2, 4, 8, 12, 18 and 24 (study-end) weeks following inclusion, during which data on alcohol consumption, depressive symptoms and general clinical well-being were recorded.

**Outcome measures**

The efficacy variables assessed included measures of alcohol consumption, depressive symptoms and quality of life. The primary efficacy parameter for alcohol consumption was the rate of relapse, defined as the intake of an average of 50 g alcohol per day for at least 3 days per week or the single intake of 100 g alcohol in a single dose.

Secondary efficacy outcomes for alcohol consumption included the rate of treatment failure (defined as the occurrence of at least three relapses as defined above during the course of the study), cumulative abstinence duration (defined as the number of days of abstinence recorded during the study) and the time to first relapse.

Depressive symptoms were assessed using the Montgomery and Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), administered at baseline and at follow-up visits at weeks 2, 4, 8, 12, 18 and 24, and the 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967), administered at baseline and at study end (week 24).

The primary efficacy parameter was the responder rate, responders being defined as those patients having a reduction of at least 50% with respect to baseline in scores on the MADRS. Secondary efficacy measures were changes in overall MADRS and HAM-D scores during the study.

Quality of life was assessed using the Spanish version of the SF-36 health-related quality of life questionnaire at inclusion and overall MADRS and HAM-D scores during the study. Study visits were programmed at 2, 4, 8, 12, 18 and 24 (study-end) weeks following inclusion, during which data on alcohol consumption, depressive symptoms and general clinical well-being were recorded.

**Safety assessments**

Adverse events, spontaneously reported by the patient or observed by the investigator, were recorded at each study visit, and vital signs measured. Each treatment emergent adverse event was rated for severity and potential implication to the study treatment, and classified according to the WHO-ART system. Blood samples were taken at inclusion, day 30 and at study end, and standard laboratory tests performed.

**Statistical analyses**

The study population analysed for efficacy was an intention to treat population, defined as all randomized patients having taken study medication at least once and having providing baseline data on primary outcome measures. Safety data was assessed for all patients having taken study medication. For alcohol consumption data, patients with missing assessments at last observation were treated as non-abstinent. For depression scale scores, missing data were handled on the principle of Last Observation Carried Forward.

Categorical variables were compared with chi-squared (χ²) test or Fisher’s exact test as appropriate. Changes in rating scores over the study period were compared by an analysis of covariance (ANCOVA), and time to endpoint variables by Kaplan–Meier survival analysis. Two-tailed comparisons were made throughout and a P-value of 0.05 was considered significant. All data were controlled and analysed centrally using the SAS Version 8.2 software package.

The sample size for the study was determined by a priori power calculations, based in previous clinical trials of acamprosate in alcohol dependence with a similar design, assuming an α risk of 0.05, a β risk of 0.20, a power of 80% and an anticipated inter-group difference of at least 20% in cumulative abstinence duration proportion. These provided an anticipated sample size of 50 patients per group.

**Results**

The study was conducted in accordance with the Declaration of Helsinki (Hong Kong Amendment), Good Clinical Practice (European Guidelines) and pertinent Spanish and Catalan legal and regulatory requirements. Written informed consent was obtained from each subject. The protocol was submitted to, and approved by, the Ethics Committee of the Hospital Clinic of Barcelona.

**Patient disposition**

Overall, 88 patients were screened for inclusion in the study, and 83 were actually randomized. These constituted the Intent to Treat population for which the efficacy data was analysed (Table 1). Thirty-seven patients withdrew prematurely from the study. The principal reasons for this were loss to follow-up (11 patients), protocol violations (nine patients) and adverse events (six patients). No other motive concerned more than five patients. Overall, 46 patients completed the protocol as planned (55%). There were no differences in rates of premature study discontinuation or in

| Table 1. Patient disposition in a study on sertraline for the prevention of relapse in detoxicated alcohol dependent patients with a comorbid depressive disorder in a randomized controlled trial in Spain |
|-------------------------------------------------|----------------|---------------|
| Patients randomized (n = 83)                     | Placebo        | Sertraline    |
| Withdrawn prior to end of treatment              | 17 (43.6%)     | 20 (45.4%)    |
| Completed treatment                              | 22 (56.4%)     | 24 (54.6%)    |

Data are presented as number of patients (%) for the intent to treat population.
protocol violations between the two treatment sets. The mean (±SD) time on study medication was 143.8 ± 10.3 days in the placebo group and 141.0 ± 9.7 days in the sertraline group.

**Patient characteristics**

The demographic and clinical characteristics of the patients at baseline are presented in Table 2. The two groups were comparable with all parameters evaluated. The demographic features of the group were typical of alcohol-dependent patients on detoxification programmes, with a mean age of 47 years, and a male predominance. Drinking history was similar between both groups, with an average dependency duration of around 16 years. Eighty-one patients fulfilled diagnostic criteria for major depression and the remaining two duration corresponded to over 80% of the total study duration. Eighty-one patients fulfilled diagnostic criteria for major depression and the remaining two duration corresponded to over 80% of the total study duration. Only 28 patients (34%) had MADRS scores at inclusion of to moderate depression. Only 28 patients (34%) had MADRS scores at inclusion of mild to moderate depression rating scales were intermediate, consistent with mild diagnostic criteria for major depression and the remaining two.

**Drinking behaviour**

Over the 6-month study period, nine patients in the placebo group (23.1%) and 14 in the sertraline group (31.8%) relapsed (Table 3). When relapse did occur, this tended to be late in the study (median time to relapse >150 days). Similar good treatment outcomes were observed on the other drinking outcome measures (Table 3). The cumulative abstinence duration corresponded to over 80% of the total study duration in both treatment groups. There were no differences between treatment groups for any of the drinking outcome measures.

**Depressive syndromes**

In terms of treatment response (≥50% improvement in the MADRS score), 39% of patients in the placebo group and 44% of patients in the sertraline group responded over the study period. There was a significant amelioration of depressive symptoms in both treatment groups as determined by scores on the MADRS and HAM-D scales (Fig. 1). Thirty-seven of the 61 patients evaluable at the last programmed study visit (24 weeks) were considered to be in remission (HAM-D score <7 at study end). There was a marginally better outcome in the sertraline group on all measures, but this was not statistically significant.

To specify any potential benefit attributable to sertraline, two subgroups of patients were analysed, corresponding to MADRS scores at inclusion above (severe depression) and below (mild to moderate depression) 26. In the former subgroup, greater overall improvement and a greater proportion of patients in remission were observed in patients receiving sertraline than in those receiving placebo (Fig. 2). On the other hand, no difference in outcome was observed in the patients with MADRS scores <26.

**Quality of life**

Concerning the quality of life data, all items of the SF-36 scale improved over the length of the study period in both of the treatment and the placebo groups (Fig. 3). In general, greater improvement was observed for mental health items than for physical health items. On the mental health item, the sertraline group improved more than the placebo group.

**Safety assessment**

The most frequently reported adverse events were headache, ‘flu-like’ symptoms and dizziness (Table 4). No difference between the two treatment groups was observed in the incidence of any of these adverse events. The incidence of gastrointestinal adverse events was low (<10% of patients).

**DISCUSSION**

Concerning drinking outcome, the principal finding of this study was the very good outcome of all patients, regardless of treatment group. Of the 83 patients included, 60 (72%) remained abstinent throughout the 6-month study period. This

<table>
<thead>
<tr>
<th>Table 2. Demographic and clinical characteristics of patients at baseline in a study on sertraline for the prevention of relapse in detoxicated alcohol dependent patients with a comorbid depressive disorder in a randomized controlled trial in Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Duration of Depression (years)</td>
</tr>
<tr>
<td>MADRS Score</td>
</tr>
<tr>
<td>HAM-D Scale Score</td>
</tr>
<tr>
<td>SF36 Physical Component Score</td>
</tr>
<tr>
<td>SF36 Mental Component Score</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Efficacy outcome measures: drinking behaviour in a study on sertraline for the prevention of relapse in detoxicated alcohol dependent patients with a comorbid depressive disorder in a randomized controlled trial in Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Relapse rate n (%)</td>
</tr>
<tr>
<td>Mean time to relapse (days) (mean ± SD)</td>
</tr>
<tr>
<td>Mean cumulative abstinence duration (days) (mean ± SD)</td>
</tr>
<tr>
<td>Cumulative abstinence duration (%)</td>
</tr>
</tbody>
</table>
somewhat surprising result can be compared with a previous randomized clinical trial performed in our centre with acamprosate (Gual and Lehert, 2001), using a very similar design, where the overall rate of complete abstinence was 40%. Similarly, for the cumulative abstinence duration proportion, we obtained a value of 0.85, compared to 0.52 (acamprosate) and 0.41 (placebo) in the previous study. However, it should be noted that the criterion of abstinence was less severe in the current study (consumption of more than 50 g of alcohol) than in the acamprosate study (any alcohol consumption at all).

We suggest that the excellent abstinence rates observed in this study may be due to the rigorous entry criteria used. Many patients with characteristics known to be determinants of poor outcome were excluded from the protocol (e.g. patients with associated substance abuse, poor motivation or other psychiatric problems). In fact, the included patients represent only a very small proportion of all the patients attending the clinic during the inclusion period who were screened for compatibility with the entry criteria (83 of 1758). The patients included may thus represent a sample with an intrinsically good prognosis. Given the high rates of abstinence in the placebo group, it was not possible to determine any extra benefit in those patients treated with sertraline. To address this question, a study could be performed in alcohol-dependent patients who are more representative of those in alcohol clinic consultation, such as those included in our acamprosate study.

No particular tolerability problems in these alcohol-dependent patients treated with sertraline were revealed in this study. In particular, there was no difference in the incidence of gastrointestinal side-effects between the two treatment groups. This is important for treatments for alcohol-dependent patients who often have impaired gastrointestinal or hepatic function.

Concerning depression, again a high degree of overall improvement was observed, and the final mean Hamilton Depression Rating Score at the end of the study was below the diagnostic threshold for syndromal depression. A similar level of response was observed in both treatment groups, consistent with the idea that depressive symptoms generally improve when patients stop drinking. The high rates of absolute abstinence found in the study may explain the good outcome on depressive symptoms. Our patients would thus correspond to patients with primary alcohol dependence and symptomatic (secondary) depression as defined by Schuckit (1985).
The recruitment of patients in an alcohol clinic environment may favour the inclusion of such patients, compared with studies where patients are recruited in a general psychiatry department. For example, in the study by Cornelius et al. (1997), where a beneficial effect of the SSRI on drinking was reported, many of the patients were admitted because they were suicidal, rather than because they were seeking help with drinking problems.

Our study does not support any particular advantage of using an antidepressant either to improve response rates or to accelerate remission in this type of patient. Nonetheless, the failure to demonstrate any added treatment benefit with sertraline may not mean that there is none. It should be noted that a significant proportion of large randomized clinical trials of SSRI in non-alcohol-dependent populations have failed to demonstrate a treatment effect, especially where there was a large placebo response. Moreover, the patients included in this study had relatively low baseline scores on depression scales at inclusion, and should be considered as suffering from mild to moderate depression. Responses to antidepressants in such alcohol-dependent patients may be less striking than in patients with more severe disease. In the study of desipramine by Mason et al. (1996), where patients were stratified according to whether they fulfilled diagnostic criteria for a major depressive episode, treatment effects on both depressive symptoms and abstinence were only observed in the major depression group. The study of fluoxetine by Cornelius et al. (1997), which of all the studies of antidepressants in alcohol dependence has demonstrated the most robust effects, initiated treatment. In such cases, sertraline offers certain advantages over other antidepressants, since it is well-tolerated, and may be useful in patients with primary depression, or more severe depression secondary to a primary alcohol dependence and will spontaneously resolve with abstinence. These patients do not benefit from sertraline treatment. On the other hand, this drug may be useful in patients with primary depression, or more severe depression, as found in the study by Roy et al. (1998). We would recommend, however, that physicians should wait at least 2 weeks to see whether symptoms resolve spontaneously before initiating treatment. In such cases, sertraline offers certain advantages over other antidepressants, since it is well-tolerated, has no active metabolites and limited impact on hepatic enzymes and can thus be used safely in patients with potentially impaired hepatic function.

REFERENCES


Table 4. Adverse events reported during a study on sertraline for the prevention of relapse in detoxicated alcohol dependent patients with a comorbid depressive disorder in a randomized controlled trial in Spain

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n = 39)</th>
<th>Sertraline (n = 44)</th>
<th>Global (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (28.2)</td>
<td>12 (27.3)</td>
<td>23 (27.7)</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>6 (15.4)</td>
<td>6 (13.6)</td>
<td>12 (14.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (12.8)</td>
<td>5 (11.4)</td>
<td>10 (12.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2 (5.1)</td>
<td>6 (13.6)</td>
<td>8 (9.6)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (7.7)</td>
<td>4 (9.1)</td>
<td>7 (8.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (7.7)</td>
<td>4 (9.1)</td>
<td>7 (8.4)</td>
</tr>
<tr>
<td>Procedure (medical/surgical/health service)</td>
<td>2 (5.1)</td>
<td>5 (11.4)</td>
<td>7 (8.4)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>4 (10.3)</td>
<td>1 (2.3)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (5.1)</td>
<td>3 (6.8)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Coughing</td>
<td>2 (5.1)</td>
<td>3 (6.8)</td>
<td>5 (6.0)</td>
</tr>
</tbody>
</table>

Only adverse events occurring in over 5% of patients overall are listed. Data are presented as absolute number of patients (%).


