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Long-term effectiveness of an intervention to discontinue chronic benzodiazepine use

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Introduction. We establish the long-term effectiveness of a brief intervention to withdraw from chronic benzodiazepine use.

Methods. Follow-up after a randomized clinical trial. Setting: Three health care centers covering 82,000 inhabitants. Subjects: 135 patients who completed the previous clinical trial (66 from the intervention group, 63 from the control group, 6 had died). Intervention-measurements: The previous clinical trial compared an intervention consisting of standardized advice and a dose tapering schedule against a control group followed by usual care. Results were evaluated at 12 months. Main outcome: benzodiazepine use three years after the end of the clinical trial, type of drug and the reason for prescription.

Results. After 3 years of follow up, 25/66 (37.9%) subjects from the intervention group and 14/63 (22.2%) from the control group were benzodiazepine free. The probability of withdrawal from benzodiazepine between patients in the intervention group was 41% higher than in the control group. Relative risk: 1.41 (95% confidence interval: 0.98-1.66). In the intervention group, 16 from 31 (51.6%) patients who had withdrawn at 12 months were benzodiazepine free after 3 years. The most prescribed benzodiazepine is lorazepam (27.9%), followed by alprazolam (12.4%) and the main reason for prescription is anxiety (16.3%) followed by anxious-depressive disorder (10.9%).

Conclusions. Even though there is a substantial relapse rate, the intervention to reduce chronic benzodiazepine use remains effective in the long-term.

Key words:
Clinical trial. Follow-up. Withdrawal. Benzodiazepine. Primary health care.

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Eficacia a largo plazo de una intervención para la deshabituación del consumo crónico de benzodiazepinas

Introducción. Se evalúa la efectividad a largo plazo de una intervención para la deshabituación del consumo crónico de benzodiazepinas.

Métodos. Diseño: seguimiento posterior al cierre de un ensayo clínico aleatorizado. Ámbito: tres centros de salud que cubren una población de 82.000 habitantes. Sujetos: 135 pacientes finalizaron el ensayo clínico previo (66 del grupo intervención, 63 del grupo control y 6 habían fallecido). Intervención-mediciones: el ensayo clínico previo comparó la eficacia de una intervención basada en una entrevista estructurada y reducción gradual de dosis frente a un grupo control con seguimiento clínico habitual. Los resultados fueron evaluados a los 12 meses. La variable principal es consumo o no de benzodiazepinas 3 años tras finalizar el estudio, principio activo y motivo de consumo.

Resultados. Tras 3 años de seguimiento, 25/66 del grupo de intervención y 14/63 del grupo control no consumen benzodiazepinas. La probabilidad de abandonar el consumo de benzodiazepinas entre los pacientes que recibieron intervención era un 41% más elevada que en el grupo control. Riesgo relativo: 1,41 (intervalo de confianza del 95%: 0,98-1,66). En el grupo intervención, 16 de los 31 (51,6%) que abandonaron el consumo a los 12 meses siguen sin consumir. La benzodiazepina más prescrita es lorazepam (27,9%) seguida de alprazolam (12,4%), y el principal motivo de prescripción es ansiedad (16,3%) seguido de trastorno mixto ansiosodepresivo (10,9%).

Conclusiones. A pesar de la importante tasa de recaída, la intervención para reducir el consumo crónico de benzodiazepinas mantiene su eficacia a largo plazo.

Palabras clave:
Ensayo clínico. Seguimiento. Deshabituación. Benzodiazepina. Atención primaria.

INTRODUCTION

Benzodiazepines are effective in the short-term treatment of anxiety disorders and insomnia but their long-term

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efficacy is questionable and exposes those who take them to a series of risks. In addition to their known capacity to produce tolerability and dependence, they have been related with increased risk of traffic accidents, increase in falls, hip fractures and memory deterioration[2-4]. The estimated prevalence of chronic use ranges from 2% to 3% of the population[5,6].

Some studies have evaluated strategies to reduce this consumption[6], these going from minimum intervention by means of a written letter with information explaining why and how to discontinue the benzodiazepine[7], a more advanced intervention with a brief informative message and gradual withdrawal regime guided by the family doctor in the out-patient clinic[1], to even other strategies accompanied by cognitive-behavior psychotherapy sessions[8,9] and/or coadjuvant drug therapy[6]. In general, these interventions are evaluated at 12 months and the withdrawal of use ranges from 18% for the intervention by letter, from 24% to 51% for the structured intervention in outpatient visit and more heterogeneous results in mixed interventions.

On the other hand, there are only a few studies that have evaluated if the efficacy of these interventions is maintained in the long term after two or three years of follow-up[4,10-12]. In one of them, it was observed that having participated in an intervention with gradual withdrawal significantly predicts the long-term maintenance without consumption[10]. And again, they coincide that there is an elevated rate of relapse among those patients who are able to discontinue taking it at 12 months since almost half have begun to use benzodiazepines again at 2 or 3 years.

In the years 2001-2003, we conducted a two-arm randomized clinical trial1 to evaluate the efficacy of an intervention. These consisted in a standardized message with gradual dose reduction regime and fortnightly follow-up visits for dishabituation of chronic use of benzodiazepines, and comparing it with a control group. The intervention was made by the patient's own family doctor. It was observed that 45% (33/73) of the intervention group patients had stopped taking benzodiazepines at 12 months versus 9% (6/66) of the control group. This means a relative risk of 4.97 (95% CI: 2.2 to 11.1).

Our current objective is to know the usage evolution of the patients who participated in the clinical trial three years after the intervention.

METHODS

Design

A follow-up at the closing of the randomized clinical trial conducted in 3 health care sites of Mallorca during the years 2001-2003 was performed.

Subjects

In order to perform the clinical trial, the patients were captured in the family doctor out-patient consultation if they met the inclusion criteria of age (from 14 to 75 years) and consumption (minimum consumption 5 days a week for at least one year). Those who had depressive or anxiety disorder under follow-up in the mental health unit, those with severe organic disease, end-stage disease, cognitive deterioration, alcoholic dependence or illegal drug consumption were ruled out. Consumption of benzodiazepines after the intervention and at 12 months were evaluated, comparing both groups.

A total of 135 out of the 139 patient who participated in the clinical trial completed it and made up the sample of the present study.

Measurements

The principal variable is consumption or not of benzodiazepines three years after completing the trial. The principle ingredient of the benzodiazepine prescribed, half life and reason why it was consumed were also analyzed, classifying it as anxiety, insomnia, mixed anxiety-depressive disorder, depressive disorder or others.

To do so, the clinical histories of the 135 patients included were reviewed, retrospectively evaluating the prescription of any benzodiazepine in the previous 6 months. Data collection was performed during the first quarter of 2006. The clinical record model used in the Balearic Islands from the year 2004 is that which forms a part of the e-Siap computer program. The data reliability is high since all of the primary care of the Balearic Islands uses the same computer program and the prescription made by any of the professionals who attend to the patient is recorded, regardless of whether it was written in the medical office or in emergency visit. The fact that a medical prescription must be obtained to dispense any benzodiazepine in the pharmacy, which makes it impossible to obtain it over-the-counter, is added to this reliability.

Statistical analysis

The SPSS statistical program for Windows, version 14.0 was used for the analysis of the data. Absolute and relative frequencies of evolution of the consumption by intervention and control groups were provided, relating them with consumption or non-consumption at 12 months. Relative risk (RR) was calculated. This measures the probability that the patients in the intervention group would not take benzodiazepines in relationship with the control group. Absolute risk reduction (ARR), understood as the difference between the percentage of patients who do not take benzodiazepines in both groups, and thus the absolute effect attributable to the

intervention, was also calculated. Finally, the number of patients needed to treat (NPT) will tell us the number of patients needed to be included in the intervention to prevent one patient from taking benzodiazepine. It is the inverse of ARR (NPT = 1/ARR). The 95% confidence interval (95% CI) was calculated for each one of the parameters. We used the program http://www.healthcare.ubc.ca/calc/clising.html in April 2007 and compared the results with those obtained at 12 months.

RESULTS

A total of 135 patients were evaluated. Of these, 6 had died, 66 belonged to the intervention group and 63 to the control group. Mean age was 64 years in the intervention group and 62 in the control group. Women accounted for 77.8% in the intervention group and 82.5% in the non-intervention group.

Three years after completing the trial 37.8% (25/66) of the intervention group and 22.2% (14/63) of the control did not take benzodiazepines versus 62.2% (41/66) of the intervention group and 77.8% (49/63) of the control group who took them. The reduction in those taking benzodiazepines that can be attributed to the intervention (ARR) was 15.6% (95% CI: 0.03% to 31.3%). The probability that the patients who received an intervention would not be taking benzodiazepines at three years was 41% greater than those who did not receive it, that is a relative risk of 1.41 (95% CI: 0.98-1.66). We observed that the number of patients needed to be given an intervention to prevent one patient from taking benzodiazepines at 3 years (NNT) is 6. In the results published in our previous work, we had observed that the probability that the intervention group patients would stop consuming benzodiazepines was much greater than in the control group (RR: 4.97) and NNT was 3.

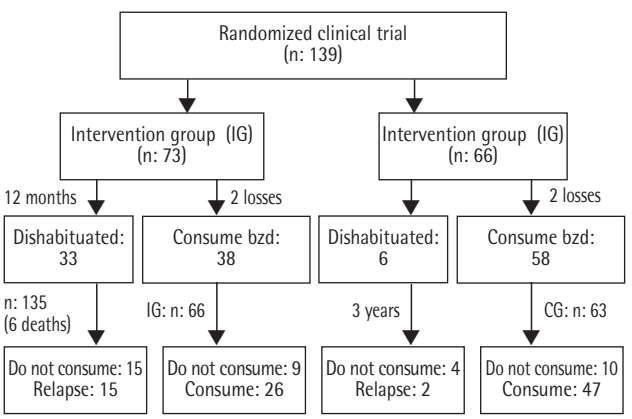

Figure 1 *Study results.*

If we compare the consumption situation at 12 months, we observe that 51.6% (16/31) of the intervention group patients who were dishabituated at 12 months have continued to not consume while 48.4% (15/31) have reinitiated consumption and that 66.6% (4/6) of the dishabituated patients at 12 months in the control group continue to be abstinent.

Parallely, 25.7% (9/35) of the intervention group who were not able to become dishabituated at 12 months are not taking it at present compared to 17.5% (10/57) of the control group.

The primary reason why benzodiazepine was prescribed during the three years of the follow-up was: anxiety (16.3%) followed by mixed anxious-depressive disorder (10.9%), depressive disorder (10.1%) and insomnia (7%). The type of benzodiazepine prescribed most is lorazepam (27.9%) followed by alprazolam (12.4%) and diazepam (7%).

No statistically significant differences have been found when making a comparison by subgroups according to the half life of benzodiazepine, possibly due to lack of contrast power.

DISCUSSION

The results of our study suggest that the efficacy of the intervention for dishabituation of chronic use of benzodiazepines is maintained in the long term, although it decreases with time. To achieve abandonment of usage of benzodiazepines at 3 years, we would need to treat twice as many patients as to achieve it at 12 months. A total of 37.8% of the patients who underwent intervention do not take benzodiazepines at three years versus 22% of the control group. However, almost half of the patients who at 12 months of the intervention were dishabituated began to take benzodiazepines again at 3 years. On the other hand, one out of every four patients who had participated in the intervention (IG) and who had not been able to withdraw at 12 months achieved this during the next three years, as did one out of every 6 from the CG. This proportion is much greater than the expected dishabituation in the usual medical consultation that is found to be between 5% and 9%[1,4]. There may be a «residual» effect since the doctors who participated in the clinical trial were not only sensitized about the subject, but had also learned to manage the withdrawal of benzodiazepines. In addition, in some way, this skill could have become incorporated into the usual practice of these professionals. We suppose that during these 3 years, they have continued to apply the intervention to their patients freely and that is why this withdrawal index greater than that expected was reached.

Study strengths and limitations

It was possible to review all of the clinical histories of each one of the 135 patients who completed the randomized clinical trial (RCT). The data reliability is high.

The primary limitation of this study is the small number of patients. The sample is not large enough to be able to perform analyses by subgroups not to establish conclusions on this level

Comparison with published works

Our results coincide in some aspects with those published up to now. Rickels et al.[11] performed a 3 year follow-up of a cohort who had followed an intervention based on gradual reduction of the dose. A total of 73% of those who had completed it successfully were consumption free at 3 years. In addition, of those who were not able to discontinue consumption after the intervention, 39% had become dishabituated during the following 3 years. Although the results are somewhat greater than those of our study, both coincide that during the 3 years of follow-up, an elevated percentage of the patients who had participated in the intervention without withdrawing from the consumption were able to do so during the 3 years of follow-up.

In two other studies, Oude Vosahar et al.[10] (2 year follow-up) and, Gorgels et al.[4] (21 month follow-up) observed that 49% and 52%, respectively, of those who did not take benzodiazepines at 12 months, continued to be consumption free at the end of the follow-up. We have found similar results in our study. Globally, what can be deduced from all the studies that have evaluated long-term benzodiazepine consumption after having participated in a gradual withdrawal program is that almost half of the patients begin to take benzodiazepines again after have stopped its consumption after the intervention. On the other hand, there is evidence that the generalized anxiety disorder, panic disorder and other anxiety disorders may have a recurrent character, so that it is to be expected the consumption will be reinitiated if the symptoms reappear.

Clinical implications of the findings obtained

The present study demonstrates that the efficacy of the intervention for the approach to dishabituation remains partially effective in the long term.

The intervention is feasible regarding time and dedication in the context of primary health care. Given that the prevalence of chronic consumption of benzodiazepines is elevated, it may be applied to a wide group of patients.

Chronic consumption of benzodiazepines has been related with cognitive deterioration, increased falls, traffic accidents and hip fractures[3]. If the intervention is applied to a considerable number of patients, we can expect a decrease in morbidity in relationship to these unfavorable effects.

In conclusion, we stress that although almost half of the patients who participated in the benzodiazepine withdrawal program and stopped consumption began to take it again during the three years of follow-up, the efficacy of the intervention lasts over time.

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