Optimization of Antidepressant Use with Pharmacogenetic Strategies

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Abstract: Background: The response rate in the pharmacological treatment of depression has been estimated to be around 50%, achieving a remission in symptomatology in only one third of the patients. Suboptimal prescription of antidepressants has been proposed as a significant explanatory factor for this therapeutic inefficacy. The use of pharmacogenetic testing might favor the optimization of pharmacotherapy in emotional disorders. However, its implementation in the clinical routine requires studies which prove its efficacy.

Objective: The aim is to explore the clinical effects obtained by means of the personalization of antidepressant treatment derived from the pharmacogenetic profile of the individual.

Method: A sample of 291 patients under antidepressant treatment was selected, and these patients were genotyped for the most common polymorphisms of the CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5 genes using RT-PCR and TaqMan® technology. 30 of them were subjected to psycho-affective assessment using the HDRS scale before and after a process of individualization of their psychopharmacological treatment in accordance with the genotype obtained.

Results: 70% of the individuals treated using the traditional criterion of trial-and-error were not taking the active ingredient most suited to their pharmacogenetic profile. The inclusion of this genetic information in the choice of drug and its dosage entails a significant, progressive reduction in depressive symptomatology, with an efficacy ratio of 80% and a remission of the pathology in almost 30% of the cases.

Conclusion: These results suggest that the prescription of pharmacogenetic profile-based strategies has a positive effect on the therapeutic response to antidepressants.

Keywords: Pharmacogenetics, Antidepressant agents, Personalized medicine, Cytochrome P450 enzymes, Depression, Therapeutic efficacy.

1. INTRODUCTION

Mood disorders represent a nosological category with a prevalence of 4-6% in the population of developed countries [1, 2]. This assortment of syndromes is made up of clinical pictures which may become markedly severe and thus entail a significant reduction in the quality of life of those affected and their environment [3, 4], an extended use of health service resources [5], considerable economic costs associated with the loss of productivity [6] and even premature deaths [7-9]. Likewise, Major Depressive Disorder (MDD), the prototypical entity in this field, occupies the fourth position among the diseases with highest morbidity and it is expected to reach the first place among the causes of disability in developed countries in the year 2030 [10]. Given the alarming clinical, social and economic cost of mood disorders, the performance of rational, quality interventions to minimize this impact is of primary importance. Pharmacotherapy stands out as the most widespread option among these approaches [11]. However, many studies have reported a high prevalence of inappropriate uses of this type of active ingredient: under-use [12-14], abuse [13, 15] or execution of non-optimal prescriptions [13, 16, 17]. To a certain extent, this could explain the low complete response rates to be found in treatment with antidepressants, which studies set at only 50 to 60% [4, 18-21], and we must bear in mind that this may entail a significant risk to the safety, well-being and day-to-day living of the patients [22].

This disturbing situation, linked to the detection of the clinical picture and its pharmacological management, highlights the need for extreme caution when prescribing antidepressants. In this context, a great many experts defend pharmacogenetics as an encouraging clinical approach. This new discipline stems from the hypothesis that the inter-individual differences observed in the response to drugs may be associated with the presence or absence of certain genetic variations [23]. Its principal objective consists of the screening of genetic polymorphisms as markers for the prediction of individual response to drugs [24, 25], enabling a more optimal selection of both the antidepressant and the dose to be em-
employed in each particular patient [26], thus reducing the incidence of possible adverse reactions [27]. Among the entire range of genetic variants, the majority of pharmacogenetic research has concentrated on the analysis of the genes encoding for the enzymes responsible for phase I and II reactions in drug metabolism, especially the genes of the cytochrome P-450 family. It is, therefore, these genes whose profile is mostly complete and is most implemented in clinical practice [28, 29], and furthermore, which take part in the metabolism of most first-line antidepressants [30], particularly the CYP2D6 gene and to a lesser extent the CYP2C19 gene [31-33]. It is postulated that the knowledge and use of this information in the choice of the active principle to be prescribed could minimize the problems which currently arise concerning pharmacological safety and therapeutic inefficacy when dealing with mood disorders [33, 34].

Consistent with this, we put forward a study with the following aims: (1) to analyze the current antidepressant drug prescription patterns in a heterogeneous population of patients attending a Medical Center specialized in Genomic Medicine and Pharmacogenomics for the first time, and to assess their suitability with regard to the symptomatology of each patient; (2) to investigate the success/fail rates resulting from the administration of antidepressants following exclusively undifferentiated clinical criteria, without taking into account the genetic idiosyncrasy of each individual in drug metabolism, and (3) to assess the potential clinical effects of the prescription of antidepressants adapted to the pharmacogenetic profile of each patient.

2. MATERIALS AND METHODS

2.1. Participants

The sample for this study comprised 1,070 patients attending the EuroEspes Biomedical Research Center (CIBE) (Bergondo, Corunna, Spain) for the first time, between 2008 and 2012. The average age was 48.32 years (SD: 21.38), with a similar proportion of men (49.2%) and women (50.8%). 54.6% of the participants presented a psychopathology compatible with some mental and/or behavioral disorder, affective syndromes appearing as one of the most prevalent categories (44.06%), together with organic mental disorders (26.26%). To meet the second aim of the study and to explore the error rate in antidepressant prescription, the selection of a sub-sample was required, which included those individuals who had been receiving antidepressant treatment during the period prior to their initial consultation at the CIBE, and of whom complete pharmacogenetic information regarding the four genotypes considered in this study was available. At this stage, the size of the resulting sample was 291 individuals, with a predominance of women (60.7%) and an average age of 55.15 years (SD: 19.07). Finally, the fulfillment of the third objective entailed the selection of a second sub-sample meeting the following inclusion criteria: a) a score equal to or higher than 8 in the Hamilton Depression Rating Scale (HDRS) at their first visit to the CIBE; b) the availability of full information on the four CYP genes considered; and c) having undergone a change in their antidepressant pharmacological pattern subsequent to the discovery of their genomic profile for the metabolism of drugs. From this target sample fraction, the participants who could not undergo assessment of their psycho-affective symptomatology for various reasons (severe cognitive deterioration, impaired communication skills, anosognosia, voluntary refusal to undergo a psychological test…) were excluded. 47.08% of the patients selected for this second sub-sample did not attend some of the follow-up sessions proposed; finally, the group comprised of 30 persons. In this case, the percentage of males (56.7%) was greater than that of females (43.3%) and the average age was 46.77 years (SD: 14.94; range: 25-76).

2.2. Procedure

2.2.1. General Procedure

At their first visit to the CIBE, and as the initial step of the protocol, each individual was informed of the possibility of using their pharmacogenetic and clinical data as part of the Center’s research projects, requesting their authorization by signing an informed consent form. Next, each patient was given a clinical interview in which, in addition to the medical information, the sociodemographic data of interest and the pharmacological pattern, which each patient was following until that moment, were collected. With this information, the corresponding specialized departments were requested to analyze the variations in the DNA sequences established for the CYP2D6, CYP2C9, CYP2C19 and CYP3A4/5 genes, and to perform the appropriate clinical tests according to each specific disease pattern. As part of these last, where appropriate, a neuropsychological assessment was requested, and in 790 cases an examination of the emotional component was required. After obtaining the results of the clinical tests, the lead physician established a new pharmaceutical treatment, bearing in mind the patient’s clinical data, the recommendations of the FDA [35], the EMA [36] and the World Guide for Drug Use and Pharmacogenomics [37], the distribution of the allelic frequencies of the aforementioned CYP genes in the Spanish population at large and the knowledge of the enzymatic biotransformation pathways of the principal active ingredients. On the majority of occasions, this treatment entailed reductions in the antidepressant dose and the avoidance of co-administration of drugs with interactive potential. Finally, the patients were given an appointment to attend the next follow-up session, set approximately one month after that time.

During the time leading up to the first follow-up session, the CIBE’s genomics laboratory carried out the genotyping of the samples and drew up the results report with its pharmacological interpretation (UM: ultra-rapid metabolizer; EM: extensive (normal) metabolizer; IM: intermediate metabolizer; PM: poor (slow) metabolizer). By means of these data it was possible to verify the appropriateness of the prior pharmacological pattern with regard to the genetic profile of the patient. The “prescriptive error” variable was defined as the prescription of antidepressants metabolized by a gene with anomalous alleles; that is, the prescription of an active ingredient for a particular patient with a UM, IM or PM phenotype of the gene responsible for the metabolism of said drug was considered to be an inappropriate pharmacological pattern.

The first follow-up session consisted of a new assessment of the patient’s clinical status (including a second admini-
stration of the HDRS scale by the neuropsychology department), the communication of the pharmacogenetic profile results, and the personalization of the pharmacological pattern, modifying it if necessary, according to the most optimal enzymatic metabolism pathway (selection of a different active principle or adjustment of the dose). Finally, the patient was summoned to a new follow-up session where the evolution of his/her clinical status was once again examined, with the aim of detecting a possible therapeutic change obtained from the individualized pharmacotherapy.

2.2.2. Psycho-affective Assessment

To assess the depressive symptomatology of the patients, the Hamilton Depression Rating Scale (HDRS) was used as a basic tool; this was applied individually by psychologists with specific training in its use. This tool is a hetero-applied scale whose aim is to explore the presence or absence of psycho-affective symptomatology, providing a quantitative assessment of the severity of the symptoms. For this study, the version in Spanish language validated by Conde and Franch [38] was selected; this comprises 21 items and presents satisfactory psychometric properties (inter-observer reliability = 0.90; convergent validity coefficient = 0.60). In accordance with Furukawa’s proposal [39], a score of 8 on this scale was taken as a cut-off point in order to detect even the mildest pictures of mental psychopathology.

2.2.3. Cytochrome P-450 Enzyme Genotyping

Each subject’s DNA was extracted from mononuclear peripheral blood cells, and 25 ng of genomic DNA from each subject was used for each multiplex SNP genotyping assay. The detection technique was based on allele-specific amplification using TaqMan® probes anchored in OpenArray® DNA microchips and Real-Time Polymerase Chain Reaction (RT-PCR)® detection. The genetic variations analyzed are described in Table 1, corresponding to 4 genes (CYP2D6, CYP2C19, CYP2C9, CYP3A4/5) which are highly involved in the metabolism of the 200 currently most-prescribed active ingredients, among these being the first-choice antidepressant agents [40, 41].

2.3. Data Analysis

With the aim of describing general pharmacoepidemiological tendencies and the prescription error rate, we performed a calculation of frequencies and percentages of the corresponding parameters (antidepressant consumption, pharmacological category and metabolism pathway, unsuitability of the pattern of the same and phenotypic distribution of the sample in the biotransformation of drugs).

To discover the therapeutic efficacy of the application of the pharmacogenetic information to the antidepressant prescription, a unifactorial repeated measures analysis of the depressive symptomatology at the three aforementioned moments in time was performed. However, given that a large majority of the sample selected did not comply with the agreed dates for the follow-up sessions, it was necessary to include the possible effect of time as a covariable in the analysis. Additionally, the efficacy ratios (ability of the pharmacological treatment to reduce the conglomerate of symptoms characterizing the emotional disorder) and remission of symptoms (HDRS <8) were found. Likewise, the t-statistic for the means difference for matched samples was calculated to study the therapeutic change obtained with the personalization of the treatment after establishing the individual pharmacogenetic profile of the patients. Finally, a simple linear regression analysis was performed to discover to what extent, subsequent to the personalization of the pharmacological treatment, the psycho-affective status could be explained by the status reached after the pharmacological protocol based on population-wide pharmacogenetic considerations.

3. RESULT

3.1. Trends in the Use of Antidepressants

Of the complete initial sample, 27.10% of the patients were following some type of antidepressant treatment prior to their arrival at the CIBE, of whom 13.46% were not diagnosed with a mood disorder after consultation at this Medical Center, following DSM-IV-TR criteria, and excluding those considered to be asymptomatic due to the effect of the medi-

| Gene       | dbsNP     | Polymorphism             | MAF   |
|------------|-----------|--------------------------|-------|
| CYP2C9     | rs1799853 | c.430C>T, p.Arg144Cys; *2 | 0.07[T]|
| CYP2C9     | rs1057910 | c.1075A>C; p.Ile359Leu; *3 | 0.04[T]|
| CYP2C19    | rs4244285 | c.681G>A; p.Pro227Pro; *2  | 0.20[A]|
| CYP2C19    | rs12248560| c.-806C>T; *17            | 0.15[T]|
| CYP2D6     | rs35742686| c.775delA; p.Arg259Glyfs; *3 | 0.01[-]|
| CYP2D6     | rs3892097 | c.506-1G>A; *4            | 0.11[T]|
| CYP2D6     | CNV       | *1xN (Dup); *5(Del)       | ———   |
| CYP2D6     | rs5030655 | c.454delT; p.Trp152Glyfs; *6 | 0.01[-]|
| CYP3A4/5   | rs776746  | c.219-237G>A; *3          | 0.31[A]|

Note: dbsNP: Single Nucleotide Polymorphism Database; MAF: minor allele frequency.
cation. Conversely, 11.4% of the individuals who were not taking antidepressants did fulfill criteria for some syndrome from the group of affective disorders. The most commonly prescribed categories of antidepressants in the case study are presented in Table 2.

94% of registered antidepressants are metabolized via enzymatic pathways corresponding to the principal genes of the **CYP-450** family (Fig. 1), whose allelic variants were spread among the sample studied, describing the phenotypic frequencies shown in Fig. (2).

### 3.2. Inappropriateness in Antidepressant Prescription

Considering only the enzymatic activity occurring during the metabolism of the antidepressants via the pathways of the 4 genes selected, an error rate of 62.19% was found in the pharmacological pattern established by the traditional trial-and-error medical criterion. The distribution of said error with regard to each of the **CYP** genes examined may be seen in Fig. (1).

### 3.3. Therapeutic Efficacy of the Inclusion of Pharmacogenetic Parameters in Antidepressant Prescription Protocols

The average HDRS scale scores of the sub-sample receiving an adjustment in their antidepressant treatment after establishing their pharmacogenetic profile are shown in Table 3.

A progressive reduction in depressive symptomatology becomes evident as pharmacological changes based on genetic information on drug metabolism are introduced, giving rise to a statistically significant trend \((F_{(i,j)} = 11.13; p = 0.002; \eta^2 = 0.284; 1-\beta = 0.896)\). A reduction in affective manifestations was observed in 80% of the cases, achieving a remission of the picture in 29.2% of the patients after only approximately 3 months.

Conversely, the time variable did not present a significant effect on the psycho-affective status of the patients throughout the aforementioned pharmacological intervention protocol \((F_{(i,j)} = 0.384; p > 0.05; \eta^2 = 0.014)\). Likewise, a significant difference in depressive symptomatology was detected subsequent to the personalized adjustment of the treatment based on the idiosyncratic genomic profile of the patients \((t_{(29)} = 26.11; p = 0.031; \eta^2 = 0.284; 1-\beta = 0.896)\), a significant correlation being found between both emotional states (pre-post personalization) \((F_{(i,j)} = 11.171; p = 0.002)\) (Fig. 3), the first serving to predict only 28.5% (coefficient of determination) of the reduction of symptoms obtained at the third application of the HDRS scale.

### 4. DISCUSSION

The first relevant datum revealed by this research is linked to the high rate of emotional disorders found in the population studied, reaching almost 25% of the same. However, given that the sample was recruited at a Medical Center specialized in Genomic Medicine and disorders of the Central Nervous System, it presents a noteworthy specificity which reduces the possibility of comparison with similar epidemiological studies. Nevertheless, we might mention that this figure quadruples that estimated for the population in general [1, 2] and is considerably lower than that calculated for the exclusively psychiatric population, which can even surpass 75%, this being the most-treated clinical category at mental health units [42, 43]. It was also found that this high prevalence of affective syndromes was being approached principally from a pharmacological viewpoint, which is synonymous with current therapeutic tendencies, as indicated by empirical evidence [11, 44]. The prescription patterns observed in case studies indicated a marked predominance of the use of selective serotonin reuptake inhibitors (SSRIs), followed at a considerable distance by selective serotonin and noradrenaline reuptake inhibitors (SSNRIs) and tricyclic antidepressants (TCA). This trend in the prescription of antidepressants presents similarities with the pattern found in research performed over the last years, both in the Spanish population [45, 46] and internationally [13, 44]. Ortiz and Lozano [47] point out as reasons for this marked predominance of SSRI consumption the better tolerability of these substances and their underlying lower dropout rates, likewise the less lethal effect which could be caused by an overdose of the same. In addition, others studies provide evidence of a significant advantage of SSRI over TCA in terms of response rate and remission rate [48] and a better acceptability of the drug [49, 50].

**Table 2. Distribution of drug groups and active ingredients most prescribed for mood disorders.**

| Pharmacologic Category | f  | %   | Most Prescribed Active Ingredients                  |
|------------------------|----|-----|-----------------------------------------------------|
| SSRIs                  | 186| 48.44| Escitalopram (61); Paroxetine (42) |
| SSNRIs                 | 70 | 18.23| Venlafaxine (37); Duloxetine (33) |
| TCAs                   | 47 | 12.34| Amitriptyline (17); Clomipramine (12) |
| Other Antidepressants  | 33 | 8.59 | Mirtazapine (24); Bupropion (4) |
| Serotonergic Modulators| 18 | 4.95 | Trazodone (18) |
| Combined Antidepressants| 16 | 4.17 | Amitriptyline + Medazepam (7); Amitriptyline + Perphenazine (7) |
| MAOIs                  | 13 | 3.39 | Rasagiline mesylate (9) |

*Note: SSRIs: Selective Serotonin Reuptake Inhibitors; SSNRIs: Selective Serotonin and Noradrenaline Reuptake Inhibitors; TCAs: Tricyclic Antidepressants; MAOIs: Monoamine Oxidase Inhibitors.*
Fig. (1). Prescription of antidepressants metabolized via enzymes encoded by genes of the *CYP* family, and error rate caused by unawareness of the pharmacogenetic profile of the patients.

Analysis of the treatment patterns established prior to arrival at the CIBE also revealed considerable rates of under-use (11.4%) and over-use (13.46%) of these drugs. Notwithstanding, prior research has described even higher ratios, with figures within a range of 20-93%, depending on the methodology and the population studied [13-15]. However, in addition to the quantitative criterion, the quality of antidepressant prescription is marked by qualitative parameters related to the suitability of the active ingredient and the dose selected [12], which is particularly complex when the health professional who must make the decisions is unaware of the pharmacogenetic profile of the patients [25]. In this regard, investigation of the polymorphic variants of the four *CYP* genes in the sample of this study revealed a marked heterogeneity among the drug-metabolizing phenotypes, the highest rates of normal enzymatic function being found in the biotransformation pathways corresponding to the *CYP3A4/5* (81.5%) and *CYP2C19* (75.33%) genes, followed by that linked to the *CYP2C9* gene (62.06%) and finally the *CYP2D6* gene (59.72%). A corresponding pattern has been described in other clinical samples [51] and in the general population [25, 41]. To continue in this vein, it is of interest to know which enzymatic pathway is followed during the metabolism of the antidepressants most commonly used in the treatment of emotional disorders. Concentrating exclusively on the role of the isoenzymes analyzed in this study, it was found that among the drugs prescribed, the highest proportion was of those metabolized via the *CYP2D6* gene pathway (36%), followed by the pathway linked to the *CYP3A4/5* gene (28%). Therefore, given the large number of antidepressants using the former metabolic pathway, which furthermore presents anomalous mutations in a high percentage of the population (> 40%), we might expect a greater probability of therapeutic inefficacy with the prescription of antidepressants acting as major substrates of the *CYP2D6* gene.

In general terms, in this study a low quality of antidepressant prescription was found when using the classical clinical criterion of trial-and-error, revealing an error rate of 62.2%. This entails a high proportion of potentially unfavorable metabolism which might be related to the marked inter-individual variability in the response to these substances [19]. Along similar lines, the epidemiological work of Kessler et al. [52] is of particular note, wherein personal interviews were carried out regarding the diagnostic and therapeutic correlates of MDD, revealing that only 41.9% of patients with depressive symptomatology were taking the appropriate active ingredient to alleviate it. Taking the compatibility of antidepressant treatment with regard to the pharmacogenetic profile as their subject matter, Hall-Flavin et al. [53] found that almost 80% of depressed patients medicated without guidance from pharmacogenetic testing were taking a drug which was not consistent with their genetic data (21% of patients were taking drugs with the warning “use with caution and more frequent monitoring”, and over 55% had prescriptions with the warning “use with caution”).

Fig. (2). Distribution of metabolizer phenotypes associated with the polymorphic variants of the *CYP* genes analyzed in the sample. *Note*: UM: Ultra-rapid metabolizer; EM: Extensive (normal) metabolizer; IM: Intermediate metabolizer; PM: Poor (slow) metabolizer.
subjects and which demonstrate the impact of pharmacogenetic testing on the efficacy of antidepressants. Hall-Flavin et al. [55] divided a sample of 227 patients with MDD into two groups previously genotyped for the most significant variants of the CYP2D6, CYP2C19, CYP1A2, SLC6A4 and HTR2A genes, and in only one of the cohorts the physician was informed of the pharmacogenetic analysis results during the antidepressant prescription phase. The depressive symptomatology remission rates were significantly lower in this group, both in the post-treatment phase and the follow-up phase up to week 8. Likewise, the patients who experienced the worst evolution were those of the group medicated by trial-and-error and who had been prescribed active ingredients which were highly discordant with their genotype. Along these lines, the work of Singh [56] highlighted that the patients who received an individualized antidepressant prescription with regard to their genotype had a 2.52 times higher probability of remission of their depressive symptoms. Winner et al. [57] found that after 10 weeks of treatment, the pharmacogenetically guided prescriptions achieved a greater response and remission rate than those treatments established by trial-and-error (Responders: 36% vs. 20.8%; Remission: 20% vs. 8.3%, respectively). However, although to a minor extent, works have also been published which indicate an absence of association between the phenotypic profiles considered and the remission rates of depressive symptomatology [59, 60]. It is therefore necessary to continue with further investigation in this regard with the implementation of blind randomized controlled trials.

CONCLUSION

These results highlight the need to introduce changes into the approach to emotional disorders. Personalization of the pharmacological treatment based on the patient’s genetic profile is proposed as an alternative with highly promising preliminary results. It seems that knowledge of certain genetic variants associated with drug metabolism aids in the prediction of the response to antidepressant treatment and the remission of symptoms, thus contributing to an improvement in the management of the disease. However, recent research has suggested the existence of other genes potentially associated with the pathogenesis of mood disorders and with the pharmacodynamics (particularly the mechanism of action) and pharmacokinetics (fundamentally metabolism and transport) of antidepressants, indicating their potential involvement in the effects of said substances and the possible adverse reactions derived from the same. It is, therefore, necessary to intensify research into genomic medicine in general and into the pharmacogenetics of antidepressants in particular, in order to continue to broaden the panorama of this dis-

Table 3. Mean scores and standard deviations in the Hamilton Depression Rating Scale (HDRS) at the three moments in time considered.

| | Pre-Treatment | Treatment adjusted to population-wide PGx parameters | Post-Treatment | Treatment adjusted to individual PGx profile |
|---|---|---|---|---|
| Depressive symptomatology (HDRS) | 15.03 | 12.53 | 10.70 |

Note: PGx: Pharmacogenetic.
cipline which, unlike trial-and-error experimentation, provides a predictive, preventive therapeutic tool aimed at the optimization of drug use, with substantial clinical benefits for the patient and economic benefits for society.

LIST OF ABBREVIATIONS

CIBE = EuroEspes Biomedical Research Center
CYP2C19 = Cytochrome P450 Family 2 Subfamily C Member 19
CYP2C9 = Cytochrome P450 Family 2 Subfamily C Member 9
CYP2D6 = Cytochrome P450 Family 2 Subfamily D Member 6
CYP3A4/5 = Cytochrome P450 Family 3 Subfamily A Member 4/5
DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
EM = Extensive (normal) Metabolizer
EMA = European Medicines Agency
FDA = Food and Drug Administration
HDRS = Hamilton Depression Rating Scale
IM = Intermediate Metabolizer
MDD = Major Depressive Disorder
PM = Poor (Slow) Metabolizer
RT-PCR = Real-Time Polymerase Chain Reaction
SSNRI = Selective Serotonin and Noradrenaline Reuptake Inhibitors
TCA = Tricyclic Antidepressants
SSRI = Selective Serotonin Reuptake Inhibitors
UM = Ultra-Rapid Metabolizer

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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