**Using pharmacokinetics and pharmacogenetics to optimize psychiatric treatments: A systematic review**

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**Objective:** Neuropsychiatrists often resort to drugs with broad inter-individual pharmacokinetic variability metabolized by highly polymorphic enzymes such as CYP2D6 and CYP2C19. Pharmacokinetics and pharmacogenetics offer considerable promise as techniques capable to allow individualized adjustments in treatments with psychoactive drugs. The purpose of this study was to review the existing evidence for the application of pharmacokinetics and pharmacodynamics to the dosing of drugs used in neuropsychiatry.

**Method:** A literature search was conducted in PubMed and Embase to find prospective studies published between January 2000 and April 2021 that used determination of psychotropic drug plasma levels or genotyping to improve response to treatment or minimize adverse events in adult patients with psychiatric conditions. MeSH terms and free search terms were used. Each article was reviewed by two independent reviewers to ensure that they met the inclusion criteria. A quantitative method was established to assess the quality of the articles selected.

**Results:** A total of 27 articles met the inclusion criteria of which 16 used pharmacokinetic and 11 pharmacogenetic techniques. Fifty percent of pharmacokinetic studies met the five predefined quality criteria. Eight of the 16 papers were on antidepressants; the remainder were on antipsychotics. Two of the latter did not find an association with efficacy or safety.

**Keywords:** Pharmacokinetics; Pharmacogenomics; Antidepressants; Antipsychotics; Review systematic; Personalized medicine.

**PALABRAS CLAVE**
Farmacocinética; Farmacogénética; Antidepresivos; Antipsicóticos; Revisión sistemática; Medicina personalizada.
None of the pharmacogenetic studies met the five quality criteria. Only one of the two studies on antipsychotics found fewer adverse events when using genomics-guided dosing in patients on CYP2D6 substrate antipsychotics. Six of the nine studies on antidepressants found that pharmacogenetics-based dosing improved efficacy.

**Conclusions:** The evidence available on pharmacokinetics and pharmacodynamics-based personalization of treatment with psychoactive drugs is scarce. Many existing studies analyze associations between genotypes and response or toxicity but provide few data on the efficacy of treatment individualization. The results obtained suggest the existence of significant differences in pharmacokinetic parameters between responding and non-responding patients, particularly in the treatment of depression. Given that the availability of pharmacogenetic information may be useful at the beginning of treatment, combining both techniques could help optimize pharmacotherapy. However, clinical trials are needed to establish their benefits with greater accuracy.

**Introduction**

Although all areas of pharmacotherapy are equally important, managing some of them can be slightly more complicated when they involve administration of drugs with broad interindividual pharmacokinetic variability, whose metabolic pathways are at times controlled by highly polymorphic enzymes such as CYP2D6 or CYP2C19. One of such areas where the management of drug therapy is often more complex is neuropsychiatry. The fact that neuropsychiatric drugs are characterized by a broad pharmacodynamic variability has hampered implementation of individualized management of such medicines. It is not unusual for terms such as precision medicine and personalized dosing to be confused. On the one hand, precision medicine, defined in the standards of national health systems as the kind of medicine that “uses information on the genes, proteins and other characteristics of the condition affecting a person to establish the diagnosis or the treatment of the said disease”, allows selecting medication in such a way that a higher likelihood of obtaining a therapeutic response is theoretically possible. On the other hand, personalized medicine also ensures that the right medication is used at the right dose in any given patient. These two concepts are confused all too frequently.

Since the 1960s and 1970s, pharmacokinetic monitoring came to be gradually— if somewhat slowly— incorporated to clinical practice. Although drugs such as diazepam, theophylline and some antibiotics have been subjected to routine monitoring in some hospitals, most centers have failed to implement any surveillance measures. Recently, with the introduction of immunopharmacotherapy to specialties such as gastroenterology, dermatology, oncology and rheumatology, there seems to have been an increase in the clinical use of pharmacokinetics, although practitioners tend to confuse monitoring with quantification and application of a widely used algorithm. Although the AGNP (Arbeitsgemeinschaft für Neuropsychopharmako- gie und PharmaKapsychiatrie) group, made up of chemists, biochemists, pharmacists and psychiatrists, published its first consensus with evidence-based recommendations for pharmacokinetic monitoring in the realm of psychopharmacology back in 2004, application of such guidelines has been very limited. Some hospitals do monitor clozapine, probably due to the restrictions on its use, but very few centers have extended their monitoring protocols to all antidepressants, antipsychotics, hypnotics and mood stabilizers.

At the same time, different platforms have been developed informing psychiatrists about the genotype of different enzyme isoforms involved in metabolic, transport and pharmacodynamic processes. Although such platforms are presented as precision medicine tools, the information they provide usually includes dosing recommendations, which gives rise to considerable ambiguity and even confusion as they are not in themselves useful tools to determine a patient’s dosing schedule. For example, although a heterozygous genotype is associated with wide phenotypic variability, with drug clearance coefficients of variation as high as 65%, it has been abundantly demonstrated that one same dose cannot lead to the same outcome in all patients. These platforms allow selection of the initial dosing regimen, albeit with a certain error margin, but they can under no circumstances be used as a basis for dosing individualization. Their dosing recommendations are usually inspired in the CPIC (Clinical Pharmacogenetics Implementation Consortium) guidelines. Apart from genetic factors, there are other elements, i.e., anthropometry, comorbidity conditions, age, etc., that play a role in the determination of medicines’ serum or plasma concentrations. As shown by several studies, their potential benefit in terms of preventing toxicity and limiting adverse events has been reported in several studies on poor metabolizers. Use of these platforms should be made in due consideration of phenocconversion, defined as a mismatch between a given genotype and its functional expression (phenotype) as a result of an interaction with a drug, a food item or a natural product. In their study on venlafaxine, Prieskorn et al. dwell extensively on this topic. It is therefore essential to carefully review the patient’s entire medication to prevent phenocconversion phenomena that could alter dosing recommendations, i.e., inclusion of bupropion in a patient on venlafaxine. The debate that has arisen on the role of pharmacokinetics and pharmacodynamics in the management of narrow therapeutic index drugs prompts us to ask the key question in this systematic review: What evidence is there on the application of pharmacokinetic or pharmacodynamic criteria to dosing in the realm of neuropsychopharmacology?

**Methods**

**Data sources and search strategy**

A systematic literature review was carried out in the PubMed and Embase electronic databases with a view to identifying all articles published between January 2000 and April 2021 that used pharmacogenetic and pharmacokinetic monitoring techniques to improve health outcomes in patients with psychiatric disorders treated with antidepressants, antipsychotics and mood stabilizers. The analysis was carried out following the PRISMA guidelines, designed to improve the quality of this kind of systematic review. An initial search was conducted in PubMed and Embase in May 2021 to identify all articles published during the above-mentioned period on the subject of interest. The search strategy is duly described in Annex I. The initial search was followed by a cross-reference search for other articles on the subject that met the inclusion criteria.

**Inclusion and exclusion criteria**

To be included, articles had to comprise adult patients over the age of 19 years diagnosed with a psychiatric disorder and treated with psychotropic drugs. Furthermore, they had to report to determination of plasma levels of the drugs employed and/or to genotyping of certain polymorphisms to improve response to treatment or minimize adverse events. Studies that only analyzed the association between one or several polymorphisms and the patients’ response to treatment or the appearance of an adverse event without providing data on the efficacy of the intervention were excluded. Inclusion and exclusion criteria are spelled out in table 1.
### Table 1. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Prospective observational studies and clinical trials published between January 2000 and April 2021.</td>
<td>- Retrospective cross-sectional studies and oral presentations at congresses.</td>
</tr>
<tr>
<td>- Performed with adult subjects &gt; 19 years diagnosed with a psychiatric condition (except autistic spectrum disorders) according to DSM or ICD criteria.</td>
<td>- Studies including less than 10 subjects.</td>
</tr>
<tr>
<td>- Inclusion of antidepressants, anti-psychotics and antiepileptics used as mood stabilizers.</td>
<td>- Studies performed on healthy volunteers.</td>
</tr>
<tr>
<td>- Use of drug plasma level determination and/or genotyping of certain polymorphisms to improve response and/or minimize adverse events.</td>
<td>- Use of plasma level monitoring only as a way of assessing adherence.</td>
</tr>
<tr>
<td>- Well performed genotyping and pharmacokinetic monitoring techniques.</td>
<td>- Studies demonstrating associations of genes or plasma levels with certain patient characteristics but not with response to treatment and/or toxicity.</td>
</tr>
<tr>
<td>- Use of clinical scales to evaluate efficacy or toxicity outcomes.</td>
<td></td>
</tr>
</tbody>
</table>

**DSM**: Diagnostic and Statistical Manual of Mental Disorders; **ICD**: International Classification of Diseases.

### Data collection process

After excluding all duplicate articles, the Mendeley computer application was used to perform a first title and abstract screen of all the articles identified, classifying them as either valid or not valid in accordance with the inclusion criteria established. The review was carried out by two independent reviewers. Discrepancies between them were resolved by consensus among all the reviewers. The articles included following this first review were read in full ensuring that the above-mentioned inclusion criteria were in fact met.

All relevant data from every study was collected to evaluate their quality and perform the subsequent analysis (condition, age, psychotropic drug, type of study, sample size, clinical scales used, methodology, length of follow-up, and concomitant treatments).

### Quality of the studies selected

A series of criteria were defined (Table 2) with the aim of objectively appraising the quality of each of the studies included. These criteria are explained below.

#### Quality criteria

1. **Patient selection.**
   - The patient sample must be homogeneous and representative of the study undertaken. The psychiatric condition analyzed and the diagnostic score used must be explicitly stated.

2. **Number of patients.**
   - At least 10 patients must be included in each experimental group, as suggested by Kloosterboer et al.¹²

3. **Effectiveness and/or safety scales.**
   - The scales employed and the respondent patient concept must be properly defined. The baseline clinical situation of each patient must be clearly defined at the outset of the study according to the scale employed. Effectiveness and safety scales must be validated and the length of follow-up must be clearly stated.

4. **Methodology:**
   - **4.1. Pharmacokinetic studies.**
     - The analytical technique employed had to be specific and sensitive, preferably based on high-resolution liquid chromatography or mass spectrometry coupled to liquid chromatography. The analytical method must be validated for reliability and reproducibility. The study must indicate the type of biological matrices used: serum, plasma or whole blood. The sampling time must be long enough to allow for a steady state to be reached and for plasma levels to be equal to the concentrations attained 10-12 hours post-administration.

5. **Concomitant treatment.**
   - Studies had to indicate the type of drugs allowed as co-medication, especially as regards any enzyme inducing or inhibiting medication that could alter the studied drug’s kinetic behavior or contribute to its pharmacokinetics.

<table>
<thead>
<tr>
<th>Code</th>
<th>Quality criterion</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient selection</td>
<td>Homogeneous characterization</td>
</tr>
<tr>
<td>2</td>
<td>Number of patients</td>
<td>≥ 10 in each experimental group</td>
</tr>
<tr>
<td>3</td>
<td>Efficacy and/or safety scales</td>
<td>Defined and validated</td>
</tr>
<tr>
<td>4</td>
<td>Methodology:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.1. Pharmacokinetic study</td>
<td>Validated analytical method, biological matrix, $C_{\text{ss}}$ ≥ $C_{\text{ss}} wider interval 10-12 h postadministration</td>
</tr>
<tr>
<td></td>
<td>4.2. Pharmacogenetic study</td>
<td>Validated genotyping method, biological matrix</td>
</tr>
<tr>
<td>5</td>
<td>Concomitant treatment</td>
<td>Indication of permitted medicines during the analysis</td>
</tr>
</tbody>
</table>

$C_{\text{ss}}$: steady-state plasma concentration; $C_{\text{ss}}$ ≥ $C_{\text{ss}}$ wider interval 10-12 h postadministration.
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On completion of the article selection process, after applying the inclusion, exclusion and quality criteria, the effect of the drugs analyzed on health outcomes was evaluated. The evaluation was based on the identification of whether any statistically significant differences were found between respondents and non-respondents, and between the presence or absence of toxicity.

Results

Application of the inclusion and exclusion criteria yielded a total of 41 articles with a proper pharmacokinetics/pharmacogenetics balance. The reviewers carried out the selection in pairs, there being four reviewers the process was divided between two groups of two reviewers each.

Article selection

Figure 1 shows the process followed to review and select the articles included in this study. Of the 899 articles initially selected, 39 were discarded after reading their title as they were duplicates of studies already included. The title and abstract screen resulted in 137 articles being exhaustively reviewed by the two pairs of reviewers. The majority of them were eventually excluded because they were association studies and did not provide any information on the efficacy of the dosing individualization techniques used. The screening process yielded a total of 31 studies, which were supplemented by another 10 articles, all of them of a pharmacogenetic nature, drawn from the literature analysis included in some of the papers selected. The final sample comprised 11 pharmacogenetic and 16 pharmacokinetic studies.

Quality of the selected articles

It must be mentioned that 50% of the pharmacokinetic studies fulfilled the five predefined quality criteria. Four studies (25%) comprised a very small patient sample with less than 10 subjects in the responding and the non-responding patient groups. Two studies (12.5%) provided no information on the length of the sampling period or on the kind of biological matrix used for the pharmacokinetic study. The description of the concomitant treatment administered during the study was not indicated in 12.5% of the papers reviewed.

The systematic search of pharmacogenetic studies eventually identified 11 papers that fulfilled the five inclusion criteria. Although the excluded studies did analyze the correlation of various genotypes with the response to treatment or the toxicity to antidepressants or antipsychotics, they did not report on any therapeutic decisions being based on genotyping or, if they did, the results of such decisions were not evaluated in terms of the efficacy or toxicity associated to the treatment. Seventy-five percent of the 11 pharmacogenetic studies selected, presented with poor genotyping quality (quality criterion 4.2) as they did not include all the genetic variants defining a given phenotype according to international guidelines because the Hardy-Weinberg principle was not complied with for the studied populations, or because no quality data was provided about the studied sample. None of the studies specified what concomitant therapy or combination of drugs was administered to each patient, making it impossible to rule out the occurrence of phenoconversion (quality criterion 5). Four studies provided no details on the scale used to measure safety (quality criterion 3) and two studies failed to define the diagnostic scale employed (quality criterion 1).

Figure 1. Process followed to review and select the articles included in this study.

<table>
<thead>
<tr>
<th>Initial search PubMed+ Embase (n = 2,373)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title review (n = 860)</td>
</tr>
<tr>
<td>Title + abstract review (n = 137)</td>
</tr>
<tr>
<td>Full article review (n = 31)</td>
</tr>
<tr>
<td>Included articles (n = 41)</td>
</tr>
<tr>
<td>Final selection after cross checking (n = 27)</td>
</tr>
</tbody>
</table>
Table 3a. Pharmacokinetic articles selected on antipsychotics used in patients with schizophrenia

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Drug</th>
<th>Follow-up design</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Results</th>
<th>Quality criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>[14]</td>
<td>Clozapine</td>
<td>PO (n = 34) 10 weeks</td>
<td>BPRS</td>
<td>C/D = 0.6 ± 0.3 ng/mL per mg (R) vs 1.0 ± 0.6 ng/mL (nR); p = 0.08</td>
<td>1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>[15]</td>
<td>Olanzapine</td>
<td>PO (n = 53) 6 weeks</td>
<td>PANSS</td>
<td>Cutoff 23.25 ng/mL</td>
<td>1, 2, 4</td>
<td></td>
</tr>
<tr>
<td>[16]</td>
<td>Nemonapride</td>
<td>PO, DF (n = 31) 3 weeks</td>
<td>BPRS</td>
<td>% improvement BPRS = 47.9 + 73.9Cp-44.2Cp² r² = 0.427, p &lt; 0.001</td>
<td>1, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>[11]</td>
<td>Risperidone</td>
<td>PO, DF (n = 30) 42 days</td>
<td>PANSS, ESRS, UKU</td>
<td>AUC ROC 55%</td>
<td>1, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>[17]</td>
<td>Aripiprazole</td>
<td>PO (n = 45) 6 weeks</td>
<td>PANSS</td>
<td>DHA 1.7 ± 11.4 ng/mL [R] vs 67.0 ± 48.4 ng/mL (nR); p = 0.023</td>
<td>1, 2, 3, 5</td>
<td></td>
</tr>
<tr>
<td>[12]</td>
<td>Fluphenazine</td>
<td>PO (n = 31) 52 weeks</td>
<td>BPRS, SANS, SAS</td>
<td>DHA 7.7 ± 2.5 ng/mL per mg/day (R) vs 4.9 ± 1.8 ng/mL per mg/day (nR); p = 0.014</td>
<td>1, 2, 3, 5</td>
<td></td>
</tr>
<tr>
<td>[13]</td>
<td>Risperidone</td>
<td>PO (n = 62) 6 weeks</td>
<td>PANSS, CGI, SAS</td>
<td>Cp = 49.9 ± 30.7 ng/mL (nR) vs Cp = 38.2 ± 17 ng/mL (R); p = 0.045</td>
<td>1, 2, 3, 4, 5</td>
<td></td>
</tr>
<tr>
<td>[18]</td>
<td>Risperidone depot</td>
<td>PO (n = 30) 6 months</td>
<td>BPRS, PANSS, CGI, SAS</td>
<td>9OH-R/RISP: 3.41 ± 1.87 [R] vs 1.6 ± 0.98 (nR); OR = 9.88; p = 0.00 (BPRS &amp; PANSS)</td>
<td>1, 2, 3, 4, 5</td>
<td></td>
</tr>
</tbody>
</table>

9OH-R: 9-hydroxy-risperidone; A: aripiprazole; ESRS: Extrapyramidal Symptom Rating Scale; FD: fixed dose; MWU: Mann-Whitney U Test; nR: non-responding patient; n.s.: no significant data; OPn: naturalistic prospective observational study; OR: odds ratio; PANSS: Positive and Negative Syndrome Scale for Schizophrenia; R: responding patient; RISP: risperidone; SANS: Scale for the Assessment of Negative Symptoms; SAS: Simpson-Agus Scale; UKU: Udvalg for Kliniske Undersøgelser Scale.

90HR: 9-hydroxy-riperidone; A: aripiprazole; AIMS: Abnormal Involuntary Movement Scale; AUC: area under the curve; BARS: Barnes Akathisia Rating Scale; BD: bipolar disorder; BPRS: Brief Psychiatric Rating Scale; CGI: clinical global impression; C/D: relationship between plasma concentration and daily dose; CMI: clomipramine; Cp: trough plasma concentration; DCMI: N-desmethylclomipramine; ESRS: Extrapyramidal Symptom Rating Scale; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; MD: major depression; nR: non-responding patient; OCD: obsessive-compulsive disorder; OR: odds ratio; PO: naturalistic prospective observational study; R: responding patient; UKU: Udvalg for Kliniske Undersøgelser Scale; YBOCS: Yale-Brown Obsessive Compulsive Scale.
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Table 4. Description of prospective clinical trials where the clinical decision was based on pharmacogenetic analyses in patients with schizophrenia and major depression

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Disease</th>
<th>Medication &amp; E/C</th>
<th>Follow-up design</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Analyzed genes</th>
<th>Analytical method</th>
<th>Results</th>
<th>Dosing recommendation/recommended drug for indication</th>
<th>Quality criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>[27]</td>
<td>Schizophrenia APs</td>
<td>123/167</td>
<td>RDBCT 12 ws</td>
<td>PANSS</td>
<td>UKU-SERS</td>
<td>CYP1A2, CYPP2C19, CYP2D6, CYP3A5</td>
<td>MassARRAY platform, TaqMan PCR</td>
<td>n.s. on PANSS; $p &lt; 0.05$ on UKU-SERS subgroups</td>
<td>% of dose modification according to dedicated protocol</td>
<td>1, 3</td>
</tr>
<tr>
<td>[28]</td>
<td>Schizophrenia APs</td>
<td>311/217</td>
<td>RDBCT 1 year</td>
<td>Persistence or treatment failure</td>
<td>UKU</td>
<td>CYP2D6, CYP2C19</td>
<td>Real time PCR (TaqMan)</td>
<td>n.s.</td>
<td>Dosing based on CYP (CPIC) guidelines</td>
<td>1, 3</td>
</tr>
<tr>
<td>[29]</td>
<td>Major depression ADs</td>
<td>352/333</td>
<td>RBDCT 12 ws</td>
<td>HDRS17</td>
<td>ND</td>
<td>CYP1A2, CYPP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, COMT, HTR2A, MTHFR</td>
<td>NeuroIDgenetix Test</td>
<td>$p &lt; 0.01$ in genotype-guided group vs control group</td>
<td>NeuroIDgenetix® test (classifies indication and dosing based on genotype)</td>
<td>1</td>
</tr>
<tr>
<td>[30]</td>
<td>Major depression ADs</td>
<td>114/113</td>
<td>POc 8 ws</td>
<td>HDRS-17</td>
<td>ND</td>
<td>CYP2D6, CYPP2C19, CYP1A2, SLC6A4, HTR2A</td>
<td>Luminex xTAG system and restriction enzymes</td>
<td>$p &lt; 0.01$ in the genotype-guided group vs standard treatment</td>
<td>Pharmacogenetics-based treatment based on GeneSight assay</td>
<td>1</td>
</tr>
<tr>
<td>[31]</td>
<td>Major depression ADs</td>
<td>22/22</td>
<td>POc 8 ws</td>
<td>QIDSC16</td>
<td>HDRS17</td>
<td>CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A</td>
<td>Luminex xTAG system and restriction enzymes</td>
<td>$p &lt; 0.01$ in the genotype-guided group vs standard treatment</td>
<td>Pharmacogenetics-based treatment based on GeneSight assay</td>
<td>1, 3</td>
</tr>
<tr>
<td>[32]</td>
<td>Depression, anxiety, ADHD, psychosis</td>
<td>178/59</td>
<td>RCT 3:1 3 months</td>
<td>NPQ SDC Interview on AEs</td>
<td>13 genes</td>
<td>Idgenetix neuropsychiatric test panel</td>
<td>Reduction of AEs at month 3; $p &lt; 0.05$ vs control</td>
<td>Medication/ dosing selection according to Idgenetix®-based genotyping (CPIC guidelines + literature)</td>
<td>2, 3, 4</td>
<td></td>
</tr>
<tr>
<td>[33]</td>
<td>Major depression ADs</td>
<td>155/161</td>
<td>RDBCT 12 ws</td>
<td>HDRS-17</td>
<td>FIBSER</td>
<td>CYP2D6</td>
<td>Real time PCR QuantStudio™ 12 K Flex Real-Time PCR System</td>
<td>$p &lt; 0.05$ in genotype-guided dosing, with HDRS reduction and FIBSER improvement</td>
<td>Recommended dosing according to Neuropharmagen pharmacogenetic report® Based on clinical guidelines and relevant literature</td>
<td>1, 3</td>
</tr>
<tr>
<td>[34]</td>
<td>Major depression ADs</td>
<td>74/74</td>
<td>RDBCT 12 ws</td>
<td>HDRS</td>
<td>ND</td>
<td>CYP2D6, CYP2C19</td>
<td>Sequenom® Matrix</td>
<td>$p &lt; 0.01$ in genotype-guided dosing, with HDRS reduction vs non-guided group</td>
<td>Recommended dosing based on CNSDose® pharmacogenetic dosing report</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 4 (cont.). Description of prospective clinical trials where the clinical decision was based on pharmacogenetic analyses in patients with schizophrenia and major depression

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Disease</th>
<th>Medication</th>
<th>E/C</th>
<th>Follow-up</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Analyzed genes</th>
<th>Analytical method</th>
<th>Results</th>
<th>Dosing recommendation/recommended drug indication</th>
<th>Quality criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>[36]</td>
<td>Major depression</td>
<td>ADs</td>
<td>26/25</td>
<td>RDBCT 10 ws</td>
<td>HDRS-17, PHQ-9, QIDS-SR, QIDS-CR</td>
<td>ND</td>
<td>CYP2D6, CYF2C19, CYF1A2, SLC6A4, HTR2A</td>
<td>Lumines xTAG system and restriction enzymes</td>
<td>n.s.</td>
<td>Recommended dosing based on GeneSight assay results</td>
<td>1</td>
</tr>
<tr>
<td>[41]</td>
<td>Major depression, ADHD</td>
<td>ADs (SSRI, SNRI, Mix, folate)</td>
<td>468 total, WT/334 risk</td>
<td>Open-label RCT 3 months</td>
<td>UKU, QUDS-SR, QHES-Q-SF</td>
<td>SLC6A4, MTHFR</td>
<td>Genecense assay</td>
<td>n.s.</td>
<td>Selection of medication base don GeneSight Report® genotyping</td>
<td>1, 3</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The present systematic review seeks to answer an apparently simple question: What are the clinical benefits of pharmacokinetics and pharmacogenetics for individualizing the dosing of psychiatric drugs? Contrary to what may be expected, the number of clinical studies on the subject is relatively scarce, which means that any conclusions drawn should be taken with caution. Over the last decade there has been a mushrooming of genetic studies aimed mainly at correlating genetic variants with exposure to psychoactive drugs. An example of this is the exhaustive review published in Molecular Psychiatry in 2004[^1]^ on the genotype-phenotype relations that exist between the different antidepressants and antipsychotics and on different dosing modification proposals intended to compensate for differences in plasma concentrations. A metaanalysis published in JAMA Psychiatry in 2012[^2]^ found a strong association between exposure to different psychoactive drugs and different CYP2C19 and CYP2D6 genotypes. These studies have led to the publication of several clinical guidelines such as the CPG (Clinical Pharmacogenetics Implementation Consortium) guidelines, the DPWG (Dutch Pharmacogenetics Working Group) guidelines, the CPNDS (Canadian Pharmacogenomics Network for Drug Safety) guidelines, and the RNPxG (French National Network of Pharmacogenetics) guidelines[^3], among others. They have also resulted in the inclusion of the relevant information in the summary of product characteristics (SmPC) of drugs like aripiprazole. These clinical guidelines made recommendations both related to indications and dose modifications based on the CYP2C19 and CYP2D6 genotypes. Nonetheless, the information selected to make such recommendations comes from studies correlating genotypes with drug exposure, which is indicative that evidence based on clinical results is too scarce to make recommendations. The information contained in these guidelines makes reference to "potential risks", suggesting that the metabolism of these drugs is subjected to the action of other genes such as CYP1A2, CYF2C9 and CYF3A4 as well as that of other environmental, epigenetic or dietary factors, comorbidities or concomitant medication[^4].

This systematic review responds to the need to analyze the clinical evidence for improving the efficacy and toxicity profile of psychoactive drugs when pharmacokinetics and pharmacogenetics are used for treatment individualization. Although clinical trials that use pharmacogenetics as a tool to individualize treatment with antipsychotics do not show significant differences regarding the effectiveness of treatment or the reduction of adverse events[^5], certain patients with a rapid or slow metabolizer CYP2D6 genotype treated with drugs metabolized by this pathway could benefit from a reduction of the dose at the beginning of their treatment[^6].

Data is less clear in the realm of clinical trials on antidepressants. It should be underscored that the nine clinical trials that use pharmacogenetics as a tool to select the right medication and individualize the dose to be administered to the patient tend to be based on different designs. None of the studies focuses on a specific antidepressant but rather they select the antidepressant to be used based on different tests and selection algorithms for each patient, which makes it difficult to draw any conclusions for any specific drug. They also use different genotyping, dose calculation and therapeutic indication algorithms such as Genecense[^7], GeneSight[^8], CNSDose[^9], Neuropharmager[^10], and Neuro IDGene[^11], in addition to the above mentioned CPG guidelines. These platforms have been approved to support physicians in their decisions on both the indication and the dosing of psychotropic drugs, establishing usage alerts for the different drugs as a function of genotype. It must be said, however, that there is wide variability across such platforms, both in terms of the number of genes analyzed and therapeutic recommendations, which makes it difficult to compare the various studies analyzed in this review. Around 40 pharmacogenetic platforms are currently being used to provide information and recommendations on the use of psychotropic drugs, which is indicative of the wide variability that exists. The review performed in this paper only found clinical trials that used live of these platforms, with negative results having been obtained with Genecense[^12].
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reported on the effects of antipsychotics in patients diagnosed with schizo-

descritas con un enfoqueนโยบาย terapéutica en la optimización de los tratamientos

As regards studies on the usefulness of clinical pharmacokinetics

Embase

PubMed

Six (#1 a #6) independent term searches were carried out using both MeSH terms and text words. The MeSH terms included were “pharmacokinetics, pharmacogenetics, pharmacogenomic variants, dose-response relationship, drug, psychotropics, antidepressants, antidepressive agents, antipsychotics, antipsychotic agents, pharmacokinetics, pharmacogenetics, therapeutic uses, therapeutic uses/pharmacokinetics, treatment outcome, adult, aged, middle aged, young adult, randomized controlled trials as topic, controlled clinical trials as topic, cohort studies, longitudinal studies, clinical trials as topic.” The free text terms used were: “pharmacokinetischen, pharmacogenoms, pharmacogenomic variants, pharmacogenic, drugg, psychotropics, antidepressants, antidepressive agents, antipsychotics, antidepressive agents, psychotropic drugs, antidepressive agents, clinical outcome, age, middle aged, young adult.”

Funding

No funding.

Conflict of interest

No conflict of interest.

Annex I

Search strategy

Embase

PubMed

Six (#1 a #6) independent term searches were carried out using both MeSH terms and text words. The MeSH terms included were “pharmacokinetics, pharmacogenetics, pharmacogenomic variants, dose-response relationship, drug, psychotropics, antidepressants, antidepressive agents, antipsychotics, antipsychotic agents, pharmacokinetics, pharmacogenetics, therapeutic uses, therapeutic uses/pharmacokinetics, treatment outcome, adult, aged, middle aged, young adult, randomized controlled trials as topic, controlled clinical trials as topic, cohort studies, longitudinal studies, clinical trials as topic.” The free text terms used were: “pharmacokinetic, pharmacogenomic, pharmacogenomic variants, pharmacogenic, drug dosage, dose-response, antidepressant, antipsychotic, antidepressive agents, psychotropic drugs, antidepressive agents, clinical outcome, treatment outcome, therapeutic uses, adult, young adult, middle aged, aged, elderly, randomized controlled trial, controlled clinical trial, cohort study, prospective.
study, longitudinal study, clinical trial). The terms were searched in the title & abstract of the articles to ensure that every article on the subject of interest was included.

#1: (((pharmacokinetic[Text Word]) OR (pharmacogenomic[Text Word]) OR (pharmacogenetic variants[Text Word])) OR (pharmacokinetics[Text Word])) OR (pharmacogenomics[MeSH Terms]) OR (pharmacogenetic[Text Word]) OR (pharmacogenomic[MeSH Terms]) OR (pharmacogenetic variants[MeSH Terms])


#3: ((((((antidepressant[Text Word]) OR (antipsychotic[Text Word]) OR (antidepressive agent[Text Word]) OR (psychotropic drugs[Text Word]) OR (anticholinergic agents[Text Word]) OR ( antidepressive agents)[MeSH Terms]) OR (antidepressive agents)[MeSH Terms]) OR (antidepressive agents)[MeSH Terms]) OR (antidepressive agents)[pharmacokinetics[MeSH Terms]) OR (antipsychotic agents)[pharmacokinetics[MeSH Terms])

#4: (((clinical outcome[Text Word]) OR (treatment outcome)[Text Word]) OR (therapeutic use)[Text Word]) OR (therapeutic use)[pharmacokinetics[MeSH Terms]) OR (treatment outcome)[MeSH Terms])

#5: (((adult[Text Word]) OR (young adult[Text Word]) OR (middle aged[Text Word]) OR (aged[Text Word]) OR (elderly)[Text Word]) OR (adult)[MeSH Terms]) OR (aged)[MeSH Terms]) OR (middle aged)[MeSH Terms]) OR (aged)[MeSH Terms])

#6: (((randomized controlled trial[Text Word]) OR (controlled clinical trial)[Text Word]) OR (controlled clinical trials)[Text Word]) OR (incidence study)[Text Word]) OR (longitudinal study)[Text Word]) OR (clinical trial)[Text Word]) OR (randomized controlled trials as topic)[MeSH Terms]) OR (controlled clinical trials as topic)[MeSH Terms]) OR (longitudinal studies)[MeSH Terms]) OR (clinical trials as topic)[MeSH Terms])

Once the six searches were completed, the items were combined giving rise to four additional searches, the process being concluded with search #11 which produced to 398 articles.

**Combined search:**

#1 AND #2 = #7

#7 AND #3 = #8

#8 AND #4 = #9

#9 AND #5 = #10

#10 AND #6 = #11

**Bibliography**


