ABCB1-Test

Optimizing pharmacotherapy of depression through genotyping

Paris, June 20, 2018
Antidepressant treatment: Current situation and how to improve

- All currently used antidepressants are unspecific pharmacologic modifications of drugs that have been on the market for over 60 years.
- Less than 1/3 of depressed patients experience a complete remission of their illness when initially treated for up to six weeks with antidepressant medications (Hall-Flavin et al., 2012).
- After several treatment trials only about 2/3 of depressed patients experience remission.
- These drugs help too few people, it takes too long until they work, and they have too many side effects.

How can we improve the situation?

Personalization based on laboratory diagnostics

- Specifically acting drugs for patients with a specific causal mechanism
- Identifying which of the current antidepressants fit best your patients genotype
- Stratifying populations with companion tests
- Pharmacokinetic testing enables precise drug selection
An antidepressant’s long journey to the target site

- Release in the gastrointestinal tract
- Resorption in the small intestine
- Blood circulation
- Liver metabolism (CYP 450 isoenzymes)
- Blood brain barrier (ABCB1)
Currently available pharmacogenetic tests to optimize depression therapy

<table>
<thead>
<tr>
<th>PHARMACOGENETIC GENE TESTS ON THE MARKET</th>
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<tbody>
<tr>
<td><strong>CYP 450</strong>*</td>
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<tr>
<td>CYP 2D6; CYP 2C19</td>
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<tr>
<td><strong>ABCB1</strong>*</td>
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<tr>
<td>rs2032583; rs2235015</td>
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<tr>
<td><strong>Multiplex gene test</strong></td>
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<tr>
<td>CYP 2D6; CYP 2C19; CYP 1A2; SLC 6A4; HTR 2A</td>
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* pharmacokinetic
** pharmacokinetic and pharmacodynamic
The blood brain barrier and the role of P-glycoprotein ("custodian molecule")
The ABCB1 gene encodes a “custodian molecule” that determines drug penetrance into the brain

- ATP-cassette subfamily member that encodes P-glycoprotein expressed in the epithelial cells of the intestine and the endothelial cells of the blood-brain barrier

- Intestinal P-glycoprotein actively transports drugs from the cell membrane back into the intestine preventing that the drug enters the blood circulation

- Blood-brain barrier P-glycoprotein prevents penetration of drugs into the central nervous system

Structure of P-glycoprotein reveals a molecular basis for polyspecific drug binding

Allen et al., Science, 2009
Schematic depiction of P-gp function depending on ABCB1-genotype and substrate property of antidepressants

Blood vessel

Blood-brain-barrier

Brain tissue

Antidepressant (■) is not a substrate of P-Glycoprotein.

Antidepressant (●) is a substrate of P-Glycoprotein (◆), encoded by the beneficial ABCB1-variant.

Antidepressant (▲) is a substrate of P-Glycoprotein (◆), encoded by the less beneficial ABCB1-variant.
Antidepressant

"Custodian molecule" encoded by ABCB1 gene

ABCB1 gene variants enable optimization of antidepressant drug treatment

❖ DNA sequence variants in the ABCB1 gene can improve prediction of individual treatment response to antidepressants

❖ These sequence variants can be detected through the ABCB1 gene test

❖ The ABCB1 test informs the physician about adequacy of antidepressant drug and dosing

❖ The gene product of the ABCB1 gene, the P-glycoprotein (P-gp), is a custodian molecule located in the blood-brain barrier

❖ P-gp is a transporter that limits the passage to the brain of many (75%) antidepressants
More patients achieve remission in shorter time with ABCB1 test guided therapy

If patients with ABCB1 gene variant 1 are treated with antidepressant P-gp substrates and plasma level monitoring *more patients achieve remission in shorter time* (Uhr et al., 2008)

* e.g. cipralex, paroxetine

** e.g. mirtazapine, agomelatine
ABCB1 guided antidepressant treatment moves away from “one size fits all” approach towards individualized medication regimes

MAJOR BENEFITS OF TESTED PATIENTS

Antidepressant drug therapy guided by ABCB1 test leads to:

❖ a better prediction of treatment success and occurrence of undesired side effects (Ray et al., 2015)

❖ higher remission rates (Breitenstein et al., 2014)

❖ and faster time until remission (Uhr et al., 2008)

REMISSION RATES OF TESTED VS. UNTESTED PATIENTS

Source: Breitenstein et al., 2014
ABCB1-genotyping allows physicians a personalized antidepressant therapy

**MAJOR BENEFITS OF TEST APPLICATION**

- ABCB1 testing allows *individualized treatment* based on latest *scientific breakthroughs*
- Patients treated under ABCB1 guidance have *higher remission rates* (Breitenstein et al., 2014)
- ABCB1 testing allows *prediction of side effect* occurrence (Ray et al., 2015) and thus better patient *compliance*
- A *meta-analysis* comprising 2695 patients from 16 studies confirms association of beneficial response and C-allele carriers $p = 0.035$. Among inpatients ($n = 485$) rs2032583 predicted beneficial outcome if treated with P-gp substrate ($p = 1.5 \times 10^{-5}$; withstanding Bonferroni correction)
Non-remission is a strong predictor for MDD recurrency – ABCB1 testing reduces health care expenses through increased remission rates

**DEPRESSION RECURRENCY IN NON-REMITTED PATIENTS**

- Patients who require more treatment steps have higher relapse rates (Rush et al., 2006)
- Non-remission of MD episode increases risk of future recurrency (Judd et al., 1998)
- Non-remission is a strong predictor of subsequent early relapse (Paykel et al., 1995)

- The risk of relapse is reduced by obtaining higher remission rates among ABCB1 tested patients that were treated according to recommendations (Breitenstein et al., 2014)
- Faster time until remission for ABCB1 variant 1 (Uhr et al., 2008) helps to reduce treatment costs and lower sick leave costs in current depressive episode
- Payers benefit from shorter periods of disablement and less illness episodes
ABCB1 Genotyping enables patient stratification and offers differential treatment algorithm

**ABCB1 GENOTYPING**

- Patient stratification is based on **individual pharmacogenetic patient profiles**

- The individual test result is accompanied by a specification of type and dose of **recommended antidepressant drug**

- In rare cases (5-8%) there is an unclear result and prioritizing SNP 2032583 is recommended
Most of the commonly prescribed antidepressants are P-gp substrates

### ANTIDEPRESSANTS THAT ARE P-GP SUBSTRATES*

- Paroxetine
- Citalopram
- Escitalopram
- Venlafaxine
- Amitriptyline
- Amitriptyline N-oxide
- Nortriptyline
- Trimipramine
- Sertraline
- Levomilnacipran
- Vilazodone
- Doxepine
- Vortioxetine
- Duloxetine (weak)
- Hypericum

### EXAMPLES FOR NON-SUBSTRATES:

- Fluoxetine
- Mirtazapine
- Agomelatine
- Bupropione
- Lamotrigine

* A P-gp substrate is a drug that is recognized by the P-gp transporter
Validation of any prognostic test requires strict adherence to study protocol

**SOURCES OF MIXED RESULTS FOR ABCB1-TESTING**

1. Outpatient vs. Inpatient
2. Multicenter trials
3. Comorbidity
4. Polypharmacy
5. Too high or too low plasma drug levels
6. Weak substrate (e.g. duloxetine)
7. Ethnic background associated with DNA variations
Scientists at the Max-Planck Institute of Psychiatry analysed 95 SNPs within the ABCB1-gene and identified 2 SNPs of particular relevance (rs2032583; rs2235015). Patients carrying the C-allele of SNP2032583 were more likely to remit than in case of the T-genotype.

A meta-analysis, comprising 16 studies with 2695 patients confirmed a high significance level ($1.5 \times 10^{-4}$) that rs2932583 in the presence of the C-genotype predicts beneficial response.

If an antidepressant drug does not act on the disease causing mechanism, it does not work, whatever the ABCB1-test informs. The ABCB1-test closes the gap between plasma drug level and bioavailability in brain tissue.
## Recommendation for the clinician*

<table>
<thead>
<tr>
<th>Reasons for poor response to AD</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1. Medication is not well resorbed from GI-tract and/or rapidly metabolized</td>
<td>Plasma drug concentration, CYP450 isoenzymes</td>
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<tr>
<td>2. Medication does not sufficiently penetrate into brain tissue</td>
<td>ABCB1-Test</td>
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<tr>
<td>3. The antidepressant mode of action does not target the specific causal mechanism</td>
<td>Switch to an AD with a different mode of action or Combination of different antidepressants, antipsychotics or mood stabilizer</td>
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</tbody>
</table>

* The Swiss Society of Anxiety and Depression (SGAD) recommends officially in their guidelines to administer the ABCB1-test for optimizing treatment of acute depression, whenever the patient fails to respond within 2-4 weeks.
Personalized Medicine: A glimpse to the future

• In the future personalized medicine will enable individual treatments that prevent development of pathology at an early stage before clinical signs occur.

PREVENTIVE MEDICINE replaces REPAIR MEDICINE

Key Players:

• Genetics and genomics (trait)
• Biomarkers (state)
• „Big-data“ – based algorithms
The Future: Paradigm Shift

Onset of disease causing pathology

Preventive intervention

Life span

Health span | Disease span

Today
Diagnosis
Therapy

Tomorrow
Early Detection
Prevention
We thank you for your interest!

Florian Holsboer