# SSRI not working?
# 7 biochemical reasons worth checking

For people whose antidepressant does not help, helps only partly, or stopped working over time.

## Why it is not your fault

An SSRI does **not make** serotonin — it only blocks its reuptake, so the serotonin your brain has produced stays in the synapse for longer. How well the drug works therefore depends on biochemistry: on the raw materials for serotonin, on methylation, on the genes that break the drug down. In the large STAR*D study only about **37%** of patients reached remission on the first SSRI. A drug that does not work is common — and often has a measurable cause.

### Never stop medication on your own

Stopping an antidepressant suddenly can cause unpleasant discontinuation symptoms and a return of depression. Make every change only with your doctor. If you have thoughts of suicide, **contact a doctor immediately or call 112**.

### First check the basics with your doctor

- Have you taken the drug **long enough** (usually 4–8 weeks) at an adequate dose?
- Do you take it **regularly**, without missing doses?
- Could **alcohol** or another drug be weakening the effect?
- Is the **diagnosis** right — could it be bipolar disorder, for example?

## 7 biochemical reasons

### 1 The body lacks material to make serotonin

Making serotonin from tryptophan requires vitamin B6 and zinc. In **pyroluria** both are lost in the urine — the SSRI then has little serotonin to hold in the synapse.

POSSIBLE SIGNS: stress sensitivity, poor dream recall, morning nausea, white spots on nails

Checked by: **Pyroluria Test · Vitamin & Mineral Test**

### 2 Overmethylation (low histamine)

According to Walsh's data, synaptic serotonin is already high in overmethylation. An SSRI can **worsen anxiety**, restlessness or insomnia.

POSSIBLE SIGNS: high anxiety, panic, agitation after starting an SSRI, chemical sensitivity

Checked by: **Histamine Test**

### 3 Undermethylation (high histamine)

An SSRI often helps at first, but the effect **fades** after months and emotional blunting appears. Raising the dose does not solve it.

POSSIBLE SIGNS: perfectionism, inner tension, obsessive thoughts, seasonal allergies

Checked by: **Histamine Test**

### 4 Copper excess and low zinc

Copper is involved in making noradrenaline. Excess copper with low zinc is linked to restlessness and insomnia that SSRIs do not target.

POSSIBLE SIGNS: hormonal mood swings, depression after childbirth or the pill, irritability

Checked by: **Vitamin & Mineral Test**

### 5 Genes that break the drug down

The enzymes CYP2D6 and CYP2C19 metabolise most SSRIs. With **fast** metabolism the drug never reaches an effective level; with **slow** metabolism side effects pile up.

POSSIBLE SIGNS: no effect even at a higher dose, or strong side effects even at a low one

Checked by: **PGx Test**

### 6 Chronic stress and cortisol

Long-term overactivity of the stress axis is linked to a weaker response to antidepressants. Stress also increases losses of zinc and B6.

POSSIBLE SIGNS: exhausted yet wired, poor sleep, morning slump or evening alertness

Checked by: **Cortisol Test**

### 7 Thyroid and missing nutrients

A sluggish thyroid and low folate, B12, vitamin D or iron can sustain depression and weaken the response to treatment.

POSSIBLE SIGNS: fatigue, feeling cold, brain fog, hair loss

Checked by: **Thyroid Test · Vitamin & Mineral Test**

## Questions for your doctor

- ☐ Could we measure zinc, copper, B6, folate and B12?
- ☐ Could my drug metabolism (CYP2D6, CYP2C19) explain why the drug is not working?
- ☐ Could my thyroid be contributing to the symptoms?
- ☐ If we change treatment, what will the plan and pace be?

## What you can do today

- **Keep a diary** of mood, sleep and side effects — once a week, on a 0–10 scale.
- **List all medicines and supplements** with doses and start dates and take the list to your doctor.
- **Complete the free 5-minute biotype questionnaire** at psylab.sk — it suggests which test makes sense first.
- **Change one thing at a time** — with several changes at once you will not know what helped.

## How PsyLab can help

**Histamine Test**
Reveals methylation status — under- or overmethylation.
**€149**

**PGx Test**
How your genes break down antidepressants. Cheek swab at home.
**€299**

**Educational consultation (60 min)**
We help you choose the right test and explain the results.
**€150**

This material is educational and does not replace medical examination or treatment. The biotypes (methylation, pyroluria, copper) are described according to the orthomolecular approach (W. J. Walsh, C. C. Pfeiffer), which is not part of standard guidelines. Decisions about treatment and any changes are made solely by a doctor.

Sources: Delgado P. L. et al., Biol Psychiatry 1999 · Rush A. J. et al. (STAR*D), Am J Psychiatry 2006 · Hicks J. K. et al. (CPIC), Clin Pharmacol Ther 2015 · Walsh W. J., Nutrient Power 2012.