Introduction

Various pharmacological strategies were proposed during the last decade to treat severe unipolar depression, among which augmentation therapies are the most common. The use of selective serotonin reuptake inhibitors (SSRI), combined with one or more mood stabilizers is well established (10). Augmentation therapies can cause several side effects and therefore benefits and risks have to be carefully balanced (12). Many drugs including SSRI, lithium, anticonvulsants or antipsychotics can reportedly cause allergic side reactions, including skin lesions (1, 5). Mood stabilizers present the highest risk for severe adverse skin reactions and the combination of such agents may considerably increase the incidence of adverse side effects (11). If these drugs are coadministered with a lipid-lowering statin therapy, which itself can cause allergic side effects (6, 8), these patients should be carefully controlled to minimize the risk to occur a life-threatening situation. We report on a depressed patient, who presented an erythematos pigmented skin rash on the whole body under combination treatment with antidepressants, atypical antipsychotic drugs, the mood stabilizer lithium and the lipid-lowering drug pravastatin. The skin rash effect was most probably due, in first line, to olanzapine, but the cutaneous skin condition was triggered and aggravated by pravastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A-(HMG-CoA)-reductase inhibitor, and lithium medication. The allergic reaction started to develop after co-administration of pravastatin. Therefore, the combination of atypical antipsychotics with statins should be carefully monitored and the benefits and disadvantages should be balanced.

Case report

The patient (female, 55 years old) was admitted to our hospital as she suffered from a severe depressive episode with psychotic auditory hallucinations, accompanied by numerous attempted suicides. The patient experienced her first depressive episode when she was 17 years old. During the preceding years, the depression aggravated and she displayed simultaneously agoraphobia and panic attacks. The frequently occurring depressive episodes were treated with several antidepressant drugs, but medication was often discontinued because of ineffectiveness or her predisposition to present adverse effects. Treatments with SSRI as paroxetine, or with mirtazapine and venlafaxine were often discontinued because of gastrointestinal side effects or insufficient therapeutic response. Because all other classical treatments failed, tricyclic antidepressants such as imipramine, trimipramine and maprotiline were prescribed during different depressive episodes in the preceding years. The patient never improved, but she displayed a higher than 10 % increase in weight within one year. Because of the severity of her depression with the presence of continuous suicidal ideation, the patient who also presented a personality disorder was unable to participate in an education group for lifestyle or perform more physical activity. Mood stabilizers such as carbamazepine, olanzapine and valproate caused mild eczematous skin lesions or strong sedation. The patient never
suffered from skin problems or any allergic diathesis in childhood.

Before admission (on day 0), the patient was polymedicated with 100 mg/day sertraline, 625 mg/day lithium carbonate, 60 mg/day aripiprazole, 200 mg/day quetiapine, 4 mg/day lorazepam, 7.5 mg/day magnesium and 0.05 mg/day levothyroxine. After admission, the dose of the antidepressant medication sertraline was increased from 100 mg/day to 150 mg/day after 2 days and to 200 mg/day after another 8 days. Because of tiredness during the day, lorazepam medication was reduced after 18 days to 3 mg/day and after 22 days to 2 mg/day after admission. Despite the high dose of aripiprazole (60 mg/day) the psychotic symptoms remained during hospitalisation. Therefore, treatment with this drug was stopped after 41 days, by a stepwise reduction of its dose (45 mg/day after 33 days; 30 mg/day after another 3

Fig. 1: Pigmented skin rash on the neck and necklin.

Fig. 2: Pigmented skin rash on the shanks.
days, and then its dose was halved every 2 till 3 days). On
day 26, lithium carbonate was increased to 900 mg/day and
on day 28, a treatment with 10 mg/day olanzapine was com-
menced. Earlier experience had shown, that this medica-
tion was of a high antipsychotic benefit to this the patient,
but it resulted also in adverse side reactions as massive
weight gain and hyperlipidemia. As there was a known fa-
mily risk for them, a statin therapy was initiated on day 29.
The psychotic symptoms decreased rapidly, but a skin le-
son was observed on day 32. On day 37, the patient pre-
pared herself with a diffuse pruritic, pigmented skin rash on
the whole body, especially on her neck, neckline and shanks
(Fig. 1 and 2). On this day, the plasma concentration of
sertraline (0.15 μmol/l) was within the recommended range
(0.03–0.16 μmol/l), while that of olanzapine (50 nmol/l)
below it (64–256 nmol/l). The fact that despite the
high dose of aripiprazole (45 mg/day on day 37), its plasma
concentration was close to the limit of quantitation (0.02
μmol/l) (recommended range: 0.2–0.67 μmol/l) suggests
poor compliance and may explain its lack of efficacy.
Pravastatin was administered during 9 days, but due its pos-
sible implication in the occurrence of these adverse effects,
its prescription was discontinued on day 38. Laboratory
findings showed a temporary serologic eosinophilia (7.1 %
and 9.6 %, days 38 and 40, respectively) (normal range:
0–6 %). The other biochemical parameters were normal, es-
specially absence of leucocytosis (7.1 x 10³/μl) (normal range:
4–10.0 x 10³/μl), no increase of C-reactive protein
(7 mg/L) (normal range: <8 mg/L) or erythrocyte sedi-
mentation rate (11 mm) (normal range: 3–11 mm).

Despite local therapy with the corticosteroid betametha-
sone, the skin rash kept the same intensity; additionally,
mild pruritic symptoms appeared in the eyes of the patient.
As a few years ago she already had a mild eczematous skin
lesion episode while treated with olanzapine, this medica-
tion was nevertheless administered for an additional time
period of 15 days (i.e. totally 21 days), with frequent lab-
oratory controls, because the suicidal ideas and psychotic
symptoms slowly disappeared. Unfortunately, the allergic
symptoms remained and medication with olanzapine had
to be stopped on day 49 of hospitalisation and replaced by
1 mg/day risperidone on the following day. Subsequently
the pruritic symptoms declined and the serologic laborato-
ry findings normalised. In particular, the skin rash symp-
toms decreased slowly during the following 18 days after
discontinuation of olanzapine medicatin till she left the
hospital but on the other hand, depressive symptoms in-
creased. Finally, this severe depressive episode required an
electroconvulsive therapy, which the patient had refused till
this term.

**Discussion**

This patient suffered from therapy-resistant and psy-
chotic depression, pronounced suicidality as well as from
a personality disorder, and presented in some stades of her
illness a questionable compliance. Polymedication was in-
dicated at her hospitalisation, comprising among other
drugs a combination of an antidepressant with an antipsy-
chotic agent, in accordance with some recent guideline (9).
Olanzapine alone might be sufficient to provoke a rash
(2, 4) since there is earlier evidence of skin problems with
this drug in this patient. Moreover, olanzapine may lead to
hyperlipidemia and other metabolic problems (7). There-
fore, especially in patients with cardiovascular risk factors,
an additional lipid-lowering therapy is recommended, which
itself can cause allergic side effects. It is well-established
that statins like pravastatin modify the composition of skin

**Graph 1:** Appearance of the pigmented skin rash.
keratin and this results in a higher vulnerability of the skin to other drugs (6, 8). As in our patient the adverse skin reaction started to develop after co-administration of pravastatin, it was probably not primarily due to olanzapine, but modifications of the skin condition by pravastatin and lithium (1) increased the risk for olanzapine to provoke it. Polymedication with aripiprazole, sertraline and quetiapine was initiated several months before hospitalisation. In the course of hospitalization the complex medication regimen was reduced and simplified. Some of the medications were discontinued. Therefore it seems improbable that these drugs significantly contributed to the adverse effect. The generalized skin reaction seems to be allergic and the temporary serologic eosinophilia developed to normal, when the pravastatin medication was stopped. Allergological skin tests as Prick-tests, Scratch-tests and Epicutaneous-tests were proposed to the patient, but reexposure to olanzapine was not performed, because she feared reappearance of a severe adverse reaction and in this critical situation of permanent suicidal ideas of the patient, these skin tests were abandoned.

In conclusion, comedication of antidepressants or antipsychotics with the lipid-lowering statin therapy should be carefully kept under surveillance and the potentiating effect of the latter for skin adverse side reactions should be recognised.

References


Corresponding author:

Dr. Alice Walder, Head of Internal Medicine, Psychiatric Hospital Sanatorium Kilchberg, Alte Landstrasse 70–84, CH-8802 Kilchberg, Switzerland; e-mail: a.walder@sanatorium-kilchberg.ch

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