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Unwanted effects of psychotropic drug interactions with medicinal products and diet supplements containing plant extracts

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Summary

Aim. Assessment of adverse drug interactions with herbal preparations (HP), i.e., plant medicines and nutritional supplements which contain plant extracts.

Method. Analysis of 147 cases of adverse events with clinical picture indicating probability or certainty of resulting from inclusion of HP into the applied pharmacotherapy (mostly psychotropic drugs).

Results. The most common effect of interactions between SSRI or SNRI antidepressants and HP were hemorrhagic complications associated with Japanese ginkgo biloba (27.45% of complications in this subgroup). Another common complication was serotonin syndrome (SS) (11.8%) occurring during the use of ginseng (one case of SS after the addition of bacopa). In the group of antipsychotic drugs, the highest number of interactions was observed in the case of haloperidol, and the highest number of complications (29.8%) was associated with ginseng (including 6 cases of ventricular arrhythmias in combination with haloperidol), milk thistle (including 7 cases of pancreatitis in combination with haloperidol or risperidone, 1 case of hepatotoxicity after adding aripiprazole) and rhodiola rosea. As for hypnotics and sedatives – interactions with ginseng were most frequently reported, mainly intensified sedative effects, cognitive disorders and disturbances in consciousness. In 132 cases, withdrawal of the plant preparation resulted in a decrease in the severity of the reported adverse reactions or a complete resolution of the described symptoms.

Conclusions. HP (especially ginseng, rhadiola rosea, ginkgo biloba, milk thistle) are associated with a significant risk of pharmacokinetic and pharmacodynamic interactions with psychotropic drugs. Because of the resulting complications and side effects, any decision to

include a herbal supplement should be preceded by a detailed safety analysis with benefit and risk assessment.

Key words: psychotropic drugs, herbal drugs, drug interactions

Introduction

Politherapy in psychiatry is often found in practice. Both psychiatrists recommend and patients without consulting the physician purchase plant medicines as well as nutritional supplements containing plant extracts, regardless of the risk of interactions with the concurrently used drugs, including psychotropic drugs [1, 2]. Even if we use 2 drugs simultaneously, we need to take into consideration the risk of adverse interactions, and if there are more than 7 drugs, the interactions will occur for sure, but the clinical picture of their consequences may vary [1–3]. As the number of preparations increases, the incidence of abnormalities in treatment is growing [4, 5]. This phenomenon includes, among others, polypharmacy (i.e., combining multiple drugs which, instead of leading to widening or enhancing therapeutic effect, is associated with the accumulation of interactions and the risk of complications), but also inadequate and insufficient use of drugs, which may consequently lead to complications and lack of expected efficacy.

Inadequate therapy means the prescription of preparations the use of which brings about a greater risk than potential benefits, and treatment not in accordance with the current medical standards [2–4]. Insufficient drug use is associated with not introducing the therapy that is recommended for the treatment or prevention of a particular disease or syndrome. It should be kept in mind that the worse the health condition of a patient, the greater the risk of polytherapy, which can become polypharmacy. Currently, we do not talk about adverse symptoms of treatment, but about problems associated with the treatment (drug related problems – DRPs). The scope of this issue includes, apart from adverse drug reactions, the need for additional treatment, the use of inadequate medications and their dosage, unnecessary treatment, induction of drug interactions. It has been clearly demonstrated that the number of DRPs increases linearly with the number of taken medicines [6].

Medicines containing plant extracts are – apart from synthetic medicines – more and more commonly used as a treatment for depression, insomnia or anxiety disorders. For example, in the available literature on the treatment of depression and/or anxiety disorders the efficacy of St. John's wort, saffron, lavandula, borage, ginseng, and rhodiola rosea [7, 8] are indicated. Because medicinal products and supplements containing plant extracts are used together with other psychotropic drugs, there is an increased risk of adverse interaction – particularly pharmacokinetic ones [7]. It is important to remember that a plant preparation can contain even a few separate pharmacologically active substances, being essentially separate drugs, which significantly increases the risk of complications. However, it is worth stressing that this issue is underestimated and rarely becomes a subject of clinical analyses [9].

Aim of the study

The aim of the study was to evaluate the incidence of adverse interactions of drugs with plant medicines and nutritional supplements containing plant extracts (HP – herbal preparations). In all patients whose medical records were included in the analysis occurred adverse events, with clinical picture indicating probability or certainty of resulting from inclusion of drugs and/or nutritional supplements containing plant extracts into the pharmacotherapy with the use of psychotropic drugs.

Material and method

In the study, 147 pharmacotherapy recommendations given to both the outpatients and hospitalized patients (94 women and 53 men) during the period between September 1, 2016 and July 30, 2017 were analyzed. The reports came from all over Poland. The mean age of women was 56 years (48–61 years), and of men – 52 years (46–58 years). Reports on the occurrence of adverse reactions being the consequence of adverse interactions between simultaneously used drugs were analyzed at the University Center for Monitoring and Research on Adverse Drug Effects, Department of Clinical Pharmacology, Jagiellonian University Medical College in Krakow. Pharmacoepidemiological analysis indicated a relationship (including causal relationship) between the pharmacological treatment and the adverse events that occurred. Pharmacodynamic and pharmacokinetic interactions and interactions associated with aggregation of side effects of simultaneous use of psychotropic drugs and HP were evaluated.

In all 147 cases, the probable (n = 15) or proven causal relationship (n = 132) was found between the addition of medication and/or nutritional supplements to the regular pharmacotherapy and the occurrence of clinical complications. As many as 86 cases were associated with the use of nutritional supplements while 61 cases resulted from the administration of plant medicines. In 132 cases, out of 147 analyzed cases, discontinuation of the plant preparation resulted in a decrease in the severity of the reported adverse reactions or a complete reversal of the symptoms.

Adverse drug interactions were evaluated in 4 groups of drugs used in psychiatry:

1) antidepressants;
2) antipsychotics;
3) anxiolytics;
4) Z-drugs.

Results

Interactions and complications in the antidepressant group (n = 51)

Tables 1–5 summarize data on antidepressant drug interactions with HP. The most commonly encountered effect of antidepressant drug interactions with HP were hemorrhagic complications resulting from the combination of serotonin reuptake inhibitors with Japanese ginkgo biloba. These were reported 14 times, accounting for 27.45% of

all complications in this subgroup. Serotonin syndrome was reported 6 times (11.8% of complications) and was a result of combination of LPD with ginseng (5 cases) or bacopa (1 case). In addition, the plants which, combined with antidepressants, most often led to interactions and complications of various character were: Japanese ginkgo biloba (14 cases – 27.45% of complications), ginseng (13 cases – 25.5%); rhodiola rosea (n = 8, 15.7%), and milk thistle (n = 6, 11.8%). Combinations of SSRIs and ginseng, milk thistle or echinacea were associated with individual cases of sexual dysfunction (priapism and/or ejaculation disorder). Two cases of ventricular arrhythmia – one resulting from the combination of escitalopram and rhadiola rosea, and the other one – sertraline and ginseng, were also observed.

Table 1. **Escitalopram interactions with drugs and nutritional supplements containing plant extracts**

Antidepressant or combination of antidepressants	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Escitalopram	2	milk thistle	cough, ejaculation disorders
Escitalopram	3	Japanese ginkgo biloba	bleeding
Escitalopram + mirtazapine	1	ginseng	serotonin syndrome
Escitalopram	2	ginseng	ejaculation disorders, priapism
Escitalopram	1	rhodiola rosea	myalgia, ventricular arrhythmia
Escitalopram + trazodone	1	rhodiola rosea	gum pain

Table 2. **Fluoxetine interactions with drugs and nutritional supplements containing plant extracts**

Antidepressant or combination of antidepressants	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Fluoxetine	3	Japanese ginkgo biloba	dizziness, hypotension, epistaxis
Fluoxetine	1	purple echinacea	intense skin pruritus, hypotension
Fluoxetine	1	bacopa	serotonin syndrome
Fluoxetine	1	ginseng	priapism
Fluoxetine + mirtazapine	2	rhodiola rosea	qualitative disturbance of consciousness, restless legs syndrome

Table 3. **Paroxetine interactions with medicinal products and diet supplements containing plant extracts**

Antidepressant or combination of antidepressants	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Paroxetine	3	Japanese ginkgo biloba	gastrointestinal, respiratory tract bleeding to CNS
Paroxetine	2	ginseng	serotonin syndrome
Paroxetine	2	rhodiola rosea	headaches, joint pain
Paroxetine + trazodone	2	carambola	headaches, worsening ejaculation disorders
Paroxetine + quetiapine	2	ginseng	neuroleptic malignant syndrome

Table 4. **Sertraline interactions with medicinal products and nutritional supplements containing plant extracts**

Antidepressant or combination of antidepressants	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Sertraline	4	Japanese ginkgo biloba	bleeding from the gastrointestinal tract, from the nose and from the genital tract
Sertraline	3	ginseng	chest pain, tachycardia, ventricular arrhythmia
Sertraline	2	purple echinacea	sudden hair loss, priapism
Sertraline	2	carambola	bruxism, headaches, aggravation of anxiety
Sertraline + mirtazapine	2	purple echinacea	serotonin syndrome
Sertraline + agomelatine	1	milk thistle	hepatotoxicity

Table 5. **Duloxetine and venlafaxine interactions with drugs and nutritional supplements containing plant extracts**

Antidepressant or combination of antidepressants	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Duloxetine	1	Japanese ginkgo biloba	bleeding from the gastrointestinal track
Duloxetine	1	ginseng	hyperhidrosis, dizziness

table continued on the next page

Duloxetine	1	St. John's wort	withdrawal syndrome, aggravation of anxiety
Duloxetine	1	milk thistle	aggravation of anxiety, headaches
Duloxetine	1	rhodiola rosea	acute throat pain, swallowing disorders
Duloxetine + sertraline	1	rhodiola rosea	diarrhea, jaundice, hepatotoxicity
Venlafaxine	1	milk thistle	hepatotoxicity, jaundice
Venlafaxine	1	ginseng	hyperhidrosis, itching of the skin

Interactions in the antipsychotic group (n = 57)

In the case of antipsychotics, the interactions resulting from their administration were observed in 4 of the analyzed cases. Tables 6–9 present data on antipsychotic drug interactions with HP. As many as 25 (43.9%) cases involved interactions with haloperidol. Among HP, the greatest number of interactions with antipsychotics and subsequent complications (n = 17, i.e., 29.8%) was associated with ginseng. Special attention should be given to 6 cases of ventricular arrhythmias (10.5% of complications in the antipsychotic group) occurring during combining it with haloperidol. 3 cases of ventricular arrhythmia were also reported when combining quetiapine and carambola. Another serious complication was pancreatitis associated with the combination of milk thistle with haloperidol (4 cases) or risperidone (3 cases) (together 12.3% of all complications in the antipsychotic group). High frequency of interaction was also observed in the combination of antipsychotics with rhodiola rosea and was it associated with a variety of symptoms (n = 9, i.e., 15.8%). In addition, in 5 patients, the combination of quetiapine and cranberry resulted in hyperhidrosis, sedation, salivation, and headache.

Table 6. **Haloperidol interactions with medicinal products and nutritional supplements containing plant extracts**

Antidepressant or combination of antidepressants	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Haloperidol	5	ginseng	hyperhidrosis, ventricular arrhythmia
Haloperidol	4	rhodiola rosea	myoclonus, hypoglycemia, sedation
Haloperidol	4	carambola	insomnia, myoclonus, dystonia

table continued on the next page

Haloperidol	4	milk thistle	pancreatitis, sedation, nausea, vomiting
Haloperidol	2	bacopa	urinary retention, SIADH
Haloperidol	2	St. John's wort	anxiety, intensification of qualitative disturbances of consciousness, delirium
Haloperidol + pernazine	1	ginseng	excessive sedation
Haloperidol + quetiapine	1	ginseng	ventricular arrhythmia
Haloperidol + olanzapine	1	rhodiola rosea	excessive sedation
Haloperidol + aripiprazole	1`	carambola	priapism

Table 7. **Quetiapine interactions with medicinal products and nutritional supplements containing plant extracts**

Antidepressant or combination of antidepressants	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Quetiapine	5	cranberry	hyperhidrosis, sedation, salivation, headaches
Quetiapine	3	carambola	sinus tachycardia, ventricular arrhythmia
Quetiapine	1	St. John's wort	insomnia, aggravation of anxiety
Quetiapine + chlorprothixene	2	ginseng	somnambulism, SIADH
Quetiapine + sulpiride	1	rhodiola rosea	priapism
Quetiapine + levomepromazine	1	ginseng	sedation, coma

Table 8. **Risperidone interactions with medicinal products and diet supplements containing plant extracts**

Antipsychotics or a combination of antipsychotics	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Risperidone	3	milk thistle	pancreatitis, nausea, vomiting, abdominal pain
Risperidone	3	ginseng	akathisia, serotonin syndrome
Risperidone	3	rhodiola rosea	catatonia, arthralgia, nausea, diarrhea

table continued on the next page

Risperidone	2	Japanese ginkgo biloba	bleeding gums, dizziness, balance disorders
Risperidone + chlorprothixene	1	bacopa	hyperhidrosis, salivation
Risperidone + sulpiride	1	Japanese ginkgo biloba	headaches, visual disturbances

Table 9. **Aripiprazole interactions with medicinal products and nutritional supplements containing plant extracts**

Antipsychotics or a combination of antipsychotics	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Aripiprazole	3	ginseng	salivation, stroke, cough
Aripiprazole	1	carambola	vaginal inflammation
Aripiprazole	1	milk thistle	hepatotoxicity, jaundice
Aripiprazole + olanzapine	1	ginseng	drowsiness, aggravation of anxiety

Interactions of anxiolytic drugs (n = 31)

Table 10 presents data on the interactions between benzodiazepine drugs and HP. Almost half of the cases were complications resulting from the combination of benzodiazepines with ginseng (n = 14, 45.2%), and they were most often associated with enhancing the effect of sedatives,, leading to excessive sedation, disturbances of consciousness and cognitive dysfunction.

Table 10. **Benzodiazepine drugs interactions with medicinal products and diet supplements containing plant extracts**

Benzodiazepine in monotherapy or in combination with other drugs	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Diazepam	5	ginseng	hallucinations, ataxia, excessive sedation
Diazepam	3	rhodiola rosea	excessive sedation, hallucinations, dizziness
Diazepam + sulpiride	2	milk thistle	nausea, vomiting, hyperbilirubinemia
Diazepam	3	carambola	excessive sedation, coma
Diazepam	2	Japanese ginkgo biloba	dizziness, visual disturbance
Clorazepate	2	ginseng	psychosis, salivation

table continued on the next page

Clorazepate	2	St. John's wort	withdrawal syndrome, seizures, aggravation of anxiety
Clorazepate + mirtazapine	2	ginseng	excessive sedation, delirium
Clorazepate + mianserin	2	ginseng	sedation, confusion, delirium
Alprazolam	2	ginseng	sedation, memory disorder
Alprazolam	1	bacopa	memory dysfunction, retrograde amnesia
Alprazolam	1	rhodiola rosea	salivation, hypotension
Alprazolam + trazodone	1	Japanese ginkgo biloba	dizziness, hypotension
Clonazepam	1	ginseng	psychosis
Clonazepam	1	rhodiola rosea	hyperhidrosis
Clonazepam	1	St. John's wort	withdrawal syndrome – aggravation of anxiety, insomnia, tremor, sinus tachycardia, hyperhidrosis

Interactions of Z-drugs (n = 8)

Table 11 shows the adverse interactions between zopiclone, zolpidem and plant preparations. Again, the most common cause was the use of ginseng preparations (n = 5, 62.5%).

Table 11. **Zopiclone and zolpidem interactions with medicinal and nutritional supplements containing plant extracts**

Hypnotic taken in monotherapy or in combination with other drugs	Number of cases	Plant active ingredient of a drug or nutritional supplement which is the cause of interaction	Clinical picture of interaction
Zopiclone	2	ginseng	NREM parasomnias
Zopiclone	1	carambola	hallucinations
Zopiclone + mianserin	1	ginseng	headache, sinus tachycardia
Zolpidem	2	ginseng	ventricular arrhythmia
Zolpidem	1	Bacopa	amnesia
Zolpidem	1	Japanese ginkgo biloba	dizziness, somnolence during the day, inability to sleep in the evening

Discussion

In our analysis in the antidepressant group, adverse drug interactions with herbal remedies were almost exclusively related to serotonin or serotonin and noradrenaline reuptake inhibitors. The most commonly encountered effect of these antidepressant drugs with HP were hemorrhagic complications and they were mainly due to the combination with Japanese ginkgo biloba (27.45% of all complications in this subgroup). Another common complication was serotonin syndrome (11.8% of complications), most commonly occurring during the use of ginseng (one case of SS after introducing bacopa). Plants which, combined with antidepressants, were most likely to interact and lead to complications of varied nature were: Japanese ginkgo biloba (27.45% of complications), ginseng (25.5%); rhodiola rosea (15.7%) and milk thistle (11.8%).

In the antipsychotics group, the highest number of interactions was observed with haloperidol, and among the herbal preparations, the highest number of interactions with antipsychotics and subsequent complications (29.8%) was associated with ginseng (including 6 cases of ventricular arrhythmia in combination with haloperidol), milk thistle (including 7 cases of pancreatitis in combination with haloperidol or risperidone and 1 case of hepatotoxicity after inclusion of aripiprazole) and rhodiola rosea.

In the group of hypnotics and sedatives, the most common interactions were those with ginseng, usually associated with the intensification of sedative effects, disturbances of consciousness and cognitive disorders. In general, up to one-third of all analyzed interactions and complications were related to the use of ginseng preparations, 15% with the use of rhodiola rosea, 14.3% – ginkgo biloba, and 10.2% – milk thistle.

In the field of the described interactions, in literature there are practically no descriptions of interactions of psychotropic drugs with milk thistle and bacopa. Single data concern the interaction of psychotropic drugs with rhodiola rosea extract. There are also no data on the interactions of benzodiazepines and Z-drugs with ginkgo extracts.

According to the presented data, drug interactions with herbal preparations are an important problem in pharmacotherapy in psychiatry. Metabolism of most psychotropic drugs which involves cytochrome P450 isoenzyme predisposes to pharmacokinetic interactions also in case of simultaneous use of psychotropic drugs and plant medicines as well as nutritional supplements that contain plant extracts (tables 12–14), [10–12].

Table 12. **Plant products included in nutritional supplements and plant medicines which are the most common cause of interaction with psychotropic drugs [11]**

A plant ingredient constituting the active substance of a medicine or nutritional supplement	Effects on cytochrome P450 isoenzymes and other important pharmacological effects	Suggested/expected action or indication for use
Milk thistle Sylibum marianum	CYP2D6, CYP3A4, CYP2C9 inhibitors	Hepatoprotective, including drug-induced hepatopathy
Rhodiola rosea	CYP2D6 inhibitor	Antidepressant and adaptogenic effects

table continued on the next page

Japanese ginkgo biloba	CYP2C9 inhibitor, antiplatelet effect that may add to the antiplatelet effect of SSRIs or SNRIs.	Flavones and flavonols contained in the plant raw material are aimed to improve CNS blood supply and mental performance as well as to reduce memory impairment; they also have antidepressant effects
Carambola Averhoa carambola	CYP3A4 inhibitor	Anxiolytic effect, strengthening the immune system, improving mental balance, rich in magnesium
St. John's wort Hypericum perforatum	CYP3A4, CYP1A2, CYP2C9 inducer, monoamine oxidase blocking	Hypericin and hyperphorine have antidepressant effects
Ginseng Panax ginseng	CYP3A4, CYP2D6 inhibitor, potentiates serotonergic tonus	Antidepressant effect, improving sexual performance
Bacopa Suttera difusa	CYP3A4 inhibitor, has a serotonergic effect	Has a sedative effect, reduces stress, has a positive effect on mood, has anxiolytic effect, improves memory
Cranberry Oxycoccus vaccinium	CYP2C9, CYP3A4 inhibitor, causes acidosis of the urine, can alter the elimination of drugs by the kidney	Urinary tract infections
Purple echinacea Echinacea purpurea	CYP3A4 inhibitor	Strengthening of immunity in patients suffering from depression

Table 13. **Antidepressants and cytochrome P450 isoenzymes [3]**

Antidepressant	Contribution of cytochrome P450 isoenzymes in drug metabolism	Cytochrome P450 isoenzymes whose activity is inhibited by the drug
Citalopram	2C19, 3A4, 2D6	
Escitalopram	2C19, 3A4, 2D6	
Fluoxetine	2D6, 2C9, 2C19, 3A4	2D6++, 2C19+, 2C9+, 3A4+
Fluvoxamine	2D6, 1A2	1A2++, 2C19++, 2C9+, 3A4+, 2D6+
Paroxetine	2D6, 3A4	2D6++, 3A4+, 1A2+, 2C9+, 2C19+
Sertraline	2C19, 2C9, 3A4	2C9+, 2C19+, 3A4+, 1A2+, 2D6+
Duloxetine	2D6, 1A2	2D6+
Venlafaxine	2D6	

Table 14. **Cytochrome P450 isoenzymes involved in the metabolism of selected antipsychotic drugs [3]**

Antipsychotics	Cytochrome P450 isoenzymes involved in drug metabolism
Haloperidol	CYP2D6, CYP3A4, CYP1A2
Risperidone	CYP2D6, CYP3A4
Quetiapine	CYP3A4
Aripiprazole	CYP2D6, CYP3A4

The presented case reports as well as previous clinical reports suggest that plant-based preparations, by inducing interactions, mainly in the pharmacokinetic mechanism, may increase the risk of adverse effects of psychotropic drugs with various clinical presentation [8, 9, 13]. During treatment with SSRIs and SNRIs, the use of preparations containing ginkgo biloba extract should be avoided because of the significant risk of hemorrhagic complications mainly due to antiplatelet effects of antidepressants and ginkgo biloba. The risk of hemorrhagic complications following serotonin reuptake inhibitors vary and depends mainly on their affinity for the serotonin transporter and the presence of other pharmacodynamic mechanisms (Table 15).

Table 15. **Use of SSRIs/SNRIs and the risk of bleeding [3, 14]**

High risk	Moderate risk	Small risk
Paroxetine Duloxetine Sertraline Fluoxetine	citalopram/escitalopram fluvoxamine venlafaxine	vortioxetine trazodone

Ginkgo preparations may further accelerate the metabolism of omeprazole and esomeprazole, primarily in the mechanism of induction of CYP2C19, and consequently reduce their efficacy in the prevention of upper gastrointestinal bleeding and may increase the risk of bleeding when taking SSRI or SNRI [7, 9, 10]. Apart from hemorrhagic complications, the literature also describe other adverse effects of combining ginkgo biloba with psychotropic treatment. Examples of such effects include single cases of coma, occurring when ginkgo biloba is combined with trazodone, and priapism in patients taking Japanese ginkgo biloba with risperidone [8, 9, 13, 15]. Ginkgo biloba reduces the concentration and efficacy of valproate. It can also reduce the anxiolytic and hypnotic effects of benzodiazepines. In our study, the combination of ginkgo biloba with hypnotics and/or anxiolytics, and in one case combination with fluoxetine, was also associated with dizziness, somnolence and hypotension [8, 9, 13, 15].

According to our analyzes and other reports, another group of preparations with high risk of interaction with psychotropic drugs are ginseng preparations. As ginkgo biloba preparations, they may increase the incidence of hemorrhagic complications after the administration of SSRIs and SNRIs, and their serotonergic effects contribute to the increased risk of serotonin syndrome [3]. Cardiac arrhythmia reported in our

analysis, which was the consequence of interaction between haloperidol and preparations including ginseng extract, may have been due to the combined effect on QTc prolongation in ECG recording [3]. Attention should also be paid to the risk of adverse effects resulting from introducing ginseng into anxiolytic and hypnotic pharmacotherapy. Apart from drowsiness and sedation, we also noted heart rhythm disturbances (single cases in combination with zopiclone or zolpidem) and psychotic symptoms (single cases in combination with clorazepate or clonazepam).

It is also worthwhile – in the case of psychotropic treatment – to avoid milk thistle extract for its hepatoprotective effect. Flavonoglycans contained in the raw material act as inhibitors against the CYP2D6, CYP3A4 and CYP2C9 isoenzymes activity and may paradoxically exacerbate hepatotoxicity of certain drugs as well as alter the risk of adverse events (including other gastrointestinal complications) [9, 13].

In Poland, there are more and more nutritional supplements and plant medicines knowledge of which is residual. An example of such a supplement is bacopa, recommended in the Ayurvedic therapies, which has a serotonergic effect, and therefore may, in conjunction with other drugs, induce the occurrence of serotonin syndrome [15]. In the analyzed material we identified one case of SS after the combination of Bacopa with fluoxetine.

The use of psychotropic drugs in combination with plant preparations may result in less frequent but significant complications and side effects, such as salivation (in our material in the case of the following combinations: quetiapine + cranberry, risperidone + bacopa, aripiprazole + ginseng) or hyperhidrosis (associated with ginseng, cranberry, bacopa, or rhodiola rosea), or vaginal inflammation (in the analyzed material – the case of combination of aripiprazole with carambola) [9, 13]. In the case of simultaneous administration of benzodiazepine and St. John's wort, one consequence of such a combination may be withdrawal syndrome as a consequence of a decrease in benzodiazepine concentrations due to enzymatic induction [1, 9]. In patients taking Z-drugs, in case of a disturbance of their metabolism by plant medicines, there may be an increased risk of NonREM parasomnias and hallucinations [9]. In the analyzed material we observed one case of hallucinations due to the combination of carambola with zopiclone and one case of memory impairment, occurring after the introduction of bacopa to zolpidem – it is especially important in the context of significant risk of complex amnestic behavioral disorders associated with zolpidem described in the literature [16].

Conclusions

Herbal preparations (especially those containing ginseng, rhodiola rosea, ginkgo biloba or milk thistle extract) are associated with a significant risk of pharmacokinetic and pharmacodynamic interactions with psychotropic drugs. Because of the resulting complications and side effects, any decision to include a herbal supplement should be preceded by a detailed safety analysis as well as benefit and risk assessment. Due to the fact that undesirable interactions occur frequently and are quite spectacular (bleeding, dystonia, excessive sedation, pancreatitis, serotonin syndrome, etc.), it is essential to

inform patients of this possibility and to indicate the actions they need to undertake after observing adverse symptoms.

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