Drug-induced hypersomnia

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Daytime somnolence may be a symptom of different somatic, neurological and psychiatric diseases and develop due to abuse and/or discontinuation of various medications. Drug-induced hypersomnia (DIH) is defined as hypersomnolence caused by the intake of multiple drugs. DIH is one of the most frequently reported effects and/or side effects of drugs. DIH prevalence varies widely and can be as high as 75% in patients receiving specific medications. DIH risk factors include elderly and senile age, impaired drug metabolism, serum drug concentration, method and frequency of drug administration, single and daily doses of drugs, etc., as in many other drug-induced diseases and syndromes. DIH can occur both due to sedative agents administration and withdrawal of psychostimulants and other activating psychotropic medications. Most often, the development of DIH is associated with the use of levodopa-carbidopa, antipsychotics, antidepressants. The pathogenesis of DIH is complex and multifactorial and is associated with the mechanism of action of individual drugs and the presence of concomitant diseases. The article discusses the risk assessment of DIH development due to various medications, diagnosis and management tactics of patients with DIH.

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Excessive daytime sleepiness is a common complaint among patients of any age. Even though lack of sleep at night is the primary and most obvious reason for such complaints, daytime sleepiness can also be a symptom of various somatic, neurological and mental diseases and be caused by drug abuse and/or discontinuation. Recurrent episodes of excessive daytime sleepiness are called hypersomnia [1, 2]. Drug-induced hypersomnia (DIH) is one of the most commonly registered adverse drug reactions. DIH has significant negative personal and social consequences for the patient, including increased risk of traffic accidents [3]. According to the 3d edition of the international classification of sleep disorders, DIH is classified as hypersomnia caused by a medication or substance [1, 2]. DIH is characterized by prolonged nighttime sleep, excessive daytime sleepiness and excessive napping [2].

DIH *diagnostic criteria* (all criteria should be present) [2]:

1. Daily periods of irresistible need to sleep or daytime lapses into sleep for more than 3 months.
2. Daytime sleepiness develops due to medication or substance administration.
3. Symptoms are not attributed to the presence of another untreated sleep disorder, somatic or neurological disease, or mental disorder.

DIH can be caused by both drugs that cause sedation and discontinuation of psychostimulants and other activating psychotropic drugs. Moreover, if psychostimulants were used to treat another disease that caused hypersomnia (for example, narcolepsy), DIH cannot be diagnosed.

Many drug classes are associated with DIH: benzodiazepines, tricyclic and tetracyclic antidepressants, monoamine oxidase (MAO) inhibitors, antihistamines, antipsychotics, etc. (see table).

Prevalence and risk factors

Hypersomnia prevalence in general populations is y 4–6%, and among patients with other sleep disorders, it can reach 30%. Hypersomnia is more frequent among men, potentially due to a higher prevalence of obstructive sleep apnea syndrome (OSAS) among them [8]. DIH is unknown. The only data available is the prevalence of DIH due to single medications (see table). For example, in patients receiving clonidine and methyldopa, it can be as high as 75%, and in lamotrigine – only 5% [8].

There is limited data on DIH risk factors. Although, as in many other drug-induced diseases and syndromes, they include elderly age, impaired drug metabolism in the liver in patients with liver diseases, impaired drug excretion in patients with kidney diseases, pharmacokinetic properties of drugs themselves, allowing them to penetrate the blood-brain barrier, serum drug concentrations, routes and frequency of drug administration, single and daily drug dose [7].

Medications associated with DIH and hypersomnia mechanisms

Medications associated with DIH and its mechanisms are summarized in the table. Here we review different drug classes.

Hypnotics

Benzodiazepine and, to a lesser degree, non-benzodiazepine hypnotics (Z-drugs) can cause DIH. Although Z-drugs have a less pronounced sedative effect than benzodiazepines, there is evidence of DIH development during their administration, especially in patients receiving high doses of zolpidem (70–390 mg) [9].

It should also be considered that benzodiazepine hypnotics can exacerbate symptoms of various sleep-related movement disorders (such as periodic limb movement disorder), leading to excessive daytime sleepiness [10].

Antidepressants

Tricyclic (amitriptyline [11] and imipramine [12]) and tetracyclic (trazodone [13] and mirtazapine [14]) sedative antidepressants are the most commonly associated with DIH. A Cochrane systematic review [11] showed a 5.5-fold increased risk of sleep disorders (including DIH) associated with amitriptyline compared to placebo. Due to the sleep-promoting effects, these medications are frequently used in insomnia treatment; however, because of their long half-live (around 7–30 h), they can also be a cause of DIH [15].

SSRIs (paroxetine, fluoxetine, and others) and SNRIs [14–16] are less often associated with DIH. Such adverse drug reactions (ADRs) are usually seen in older patients [16].

Antipsychotics

DIH associated with antipsychotics most likely develops due to histamine, α_1-adrenergic or $5HT_2$-receptors stimulations, rather than their impact on the dopamine D2 receptors [15]. Among antipsychotics, clozapine has the greatest sedative effect. Quetiapine, olanzapine, and chlorpromazine have a moderate sedation potential, while risperidone, haloperidol, aripiprazole, and ziprasidone have the least sedative effect [17]. On the other hand, the CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness) [18] did not reveal significant differences in DIH prevalence among patients treated with olanzapine, quetiapine, risperidone, perphenazine, or ziprasidone.

Anticonvulsants

Somnolence is one of the most common ADRs of anticonvulsants [15].

DIH associated with sodium channel blocking anticonvulsants (carbamazepine, phenytoin, etc.) does not occur as often as with the use of barbiturates. Besides, many antiepileptic drugs have several mechanisms of action, which may lead to DIH development. Drug dose and titration period, along with the number of anticonvulsants, may also con-

Medications associated with DIH [4–6]

Drug classes and agents	Prevalence, %	Mechanisms of action	Level of evidence
		Hypnotics	
Benzodiazepines:			
triazolam	10–25	GABA receptor	B
flurazepam	10–25	agonist	B
Non-benzodiazepine:			
zolpidem		GABA	B
zaleplon	Unknown	receptor	B
zopiclone		agonist	B
		Antidepressants	
Tricyclic:			
amitriptyline	20–45	H1-receptors antagonist, anticholinergic activity	A
imipramine	5–23		A
Tetracyclic:			
mirtazapine	10–53	H1- и $5HT_{2a}$-receptors antagonist	A
trazodone	8	$5HT_{2a}$-receptors antagonist	A
MAO inhibitors:			
phenelzine	Unknown	Decrease in norepinephrine, serotonin, and dopamine levels due to MAO suppression	B
SSRIs:			
escitalopram	4,9–36		A
fluvoxamine	14–26	Inhibition	A
fluoxetine	5–18	of serotonin	A
paroxetine	2–21	reuptake	A
sertraline	7–13		B
SNRIs:			
venlafaxine	13–31	Inhibition of serotonin	A
duloxetine	12,6	and norepinephrine reuptake	B
Others:			
doxepin	Unknown	Inhibition of biogenic amines neuronal reuptake (norepinephrine, serotonin), central H1-receptors antagonist, cholinolytic and α1-adrenergic activity	B
		Antipsychotics	
Haloperidol	25		A
Thioridazine	Approximately 25	H1-receptors antagonist	A
Chlorpromazine	33		A
		Atypical antipsychotics	
Clozapine	52	H1-receptors antagonist,	A
Risperidon	17–22,6	serotonin receptor agonist	A
Paliperidone	17,9		A
Aripiprazole	15 mg – 42; various data – 18–25		A
Olanzapine	18–31		A
Asenapine	6–10		A
Quetiapine	16–31		A
Ziprasidone	16–24		A
Perphenazine	28		A

tribute to DIH. Thus, DIH was significantly more frequent in patients receiving rufinamide 1600 mg/day [19], topiramate 400–1000 mg/day [20]. In an analysis of six randomized controlled trials [21], DIH was the second most common adverse event in the topiramate group. When a second anticonvulsant was added, DIH became the leading ADR. At the same time, in patients administered with topiramate monotherapy, especially with low starting dosage (50 mg/day) and slow weekly dosage increments (50 mg/week), DIH incidence was lower [22].

Finally, daytime sleepiness in patients with epilepsy receiving anticonvulsants may be associated with nocturnal seizures, poor sleep hygiene, and the presence of concomitant sleep disorders (such as OSAS or restless legs syndrome) which should also be considered.

Dopaminergic drugs

The use of dopamine receptor agonists is considered to be one of the reasons for hypersomnia in patients with Parkinson's disease [23]. However, we should keep in mind that daytime sleepiness mechanisms in Parkinson's disease are much more complex and include degeneration of various structures necessary for the normal maintenance of the sleep-wake cycle, and the fact that up to 80% of patients have various concomitant sleep disorders [24].

DIH associated with dopaminergic medications frequently develops during the titration period and can become less severe in patients on a stable dose. Excessive daytime sleepiness is more common if dopamine receptor agonists are combined with levodopa [24].

Other medications

α- and β-receptors blockers. DIH usually occurs in patients prescribed with central acting α_2-receptors agonists (clonidine and methyldopa). Furthermore, β-blockers, which have an additional α_1-blocking effect (carvedilol and labetalol, the last one is not registered in Russia), are also associated with DIH [25].

Dexamethasone. Both DIH and insomnia can develop in children treated with high doses of dexamethasone [26].

Evaluation

The Epworth sleepiness scale can be used as a screening tool to assess daytime sleepiness [27]. An objective method to evaluate daytime sleepiness is the multiple sleep latency test. Polysomnography is necessary if there is a suspicion of concomitant sleep disorders (e.g., OSAS) [28].

As no specific scales exist for the DIH evaluation, it is necessary to carefully collect the patient's history and analyze all prescribed medications using a special algorithm [7, 29]. The Naranjo scale should be used to determine the causal relationship between drug intake and the development of hypersomnia [30].

Continuing of Table

Drug classes and agents	Prevalence, %	Mechanisms of action	Level of evidence
Anticonvulsants			
Lamotrigine	5	Decrease neuronal excitability by various mechanisms	A
Phenytoin	5–10		A
Topiramate	5–27		A
Levetiracetam	6,3–10		A
Carbamazepine	5–10		A
Gpabapentin	5–15		B
Pregabalin	5–15		B
Zonisamide	5–15		B
Rufinamide	12		A
Dopaminergic drugs			
Carbidopa/Levodopa	75	Dopamine receptors agonist	B
Selegiline	10–32	Decrease neuronal excitability by various mechanisms	B
Amantadine	14	Unknown	B
Other medications			
β- and α1-receptors blockers:			
carvedilol	3–11	β- and α1-receptors antagonists, melatonin production suppression	A
labetalol*	1–4		A
α2-receptors agonists:			
clonidine	30–75	α2-receptors agonists	B
methyldopa	30–75		B
Corticosteroids:			
dexamethasone	Unknown	Multiple effects on the hypothalamic-pituitary-adrenal system; decreased release of corticotropin-releasing hormone, which activates locus coeruleus and thus the norepinephrine system, which in turn increases the wakefulness level	B
Antihistamines:			
loratadine	30 compared with 20 in placebo group (combination therapy with pseudo-ephedrine)	Peripheral histamine H1-receptors antagonist	A

Note. GABA – gamma-Aminobutyric acid; H1-receptor – histamine H1-receptor; 5HT2a – a subtype of the serotonine receptors, i.e. receptors that endogenous neurotransmitter serotonin binds to (5-hydroxytryptamine, 5-HT); SSRIs – selective serotonin reuptake inhibitors; SNRIs – serotonin–norepinephrine reuptake inhibitors. Levels of evidence [7]: A – one or several randomized controlled trials, B – non-randomised controlled studies, prospective observational studies, cohort studies, retrospective studies, case-control studies, meta-analysis and/or postmarketing studies; C – one or several case reports or case series.

Tactics

The most rational tactic in patients with DIH is the withdrawal of a causative agent. Gradual, controlled withdrawal is the optimal strategy for sedative medications (e.g., benzodiazepine hypnotics, tricyclic antidepressants). It is also possible to replace the drug that caused DIH with medications from a different drug class with a less pronounced sedative effect to prevent or decrease the severity of withdrawal syndrome [2]. In patients with epilepsy receiving anticonvulsants, it may be appropriate to monitor the plasma drug concentration. In patients with Parkinson's disease, lowering the dose of levodopa can sometimes eliminate DIH [24]. In case of identification and withdrawal of the drug that caused DIH, patients have a favorable prognosis.

Conclusion

DIH is a side effect of several drugs that is largely unknown by medical practitioners. The use of a large number of medications is associated with DIH development. Raising the awareness of doctors of different specialties about this ADR, timely adjustment of drug regimens, and possible withdrawal of drugs that caused DIH and the DIH prevention are essential for the quality of life and safety of the patient.

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