FACING ADHD TOGETHER

Current Perspectives on Drug Interactions in Pharmacotherapy

Eva Döring-Brandl

Patients with psychiatric disorders commonly receive multiple medications due to non-response, necessary augmentation and relevant psychiatric or somatic comorbidities. This can result in clinically relevant drug-drug interactions with potentially harmful side effects. Therefore, knowledge on potential interactions and their mechanisms is crucial for all clinicians prescribing psychiatric medication. In a very stimulating talk at the Meet the Expert Online Seminar, Dr. Eva Döring-Brandl shared various practical insights for routine care of ADHD, comorbid conditions and polypharmacy.

KEY STATEMENTS

- Drug-drug interactions can significantly change efficacy and increase the risk of side effect of many medications used in psychiatric treatment.
- Cytochrome enzymes are highly relevant in pharmacokinetic interactions.
- Co-medication with high risk of drug-drug interaction needs to be carefully considered when prescribing ADHD medication.
- Always ask ADHD patients about illegal drug use and over-the-counter medication.

ADHD and polypharmacy

"Comorbidities can lead to prescription of polypharmacy."

An understanding of the key mechanisms underlying drug-drug interactions is essential for recognizing their clinical implications. Many individuals with ADHD experience a range of psychiatric and somatic comorbidities that require treatment alongside their ADHD management. The possible presence of comorbidities in ADHD patients can exibit polypharmacy. The WHO defines polypharmacy as 5 or more concurrent medications, including over-the-counter (OTC) drugs, however, more than 100 different definitions for polypharmacy exist in literature.[1] Dr. Döring-Brandl emphasized that polypharmacy is not inherently negative. In many cases, it is either explicitly recommended or unavoidable. For instance, the presence of a psychiatric comorbidity often necessitates the use of multiple medications.

Drug-Drug-interactions

"The risk for drug-drug interactions increases with the number of medications."

The risk for drug-drug interactions increases with the number of medications. With approximately 2,200 available medications in Germany, there are more than 2,4 million possible interactions between 2 medications.[2] Drug-drug interactions can be pharmacokinetic, meaning everything about how the body affects medication, or they can be pharmacodynamic, meaning everything that the drug does to the body. In general, drug-drug interactions can lead to increased or reduced efficacy of one of the drugs, as well as to an increased risk of side effects.

Pharmacokinetic interactions and cytochrome enzymes

"The CYP2D6 enzyme is particularly important for drug-drug interactions in psychopharmacology."

Pharmacokinetic interactions are particularly relevant in psychopharmacology. Most types of psychiatric medications are metabolised by cytochrome enzymes. A third of medications are metabolised by the CYP4A4/5 enzyme. The CYP2D6 enzyme plays a crucial role in psychopharmacological drug-drug interactions, as it metabolizes approximately 20% of all medications. CYP2C19 is crucial for the metabolism of many antidepressants and some antipsychotics, but in general, only 6 to 10% of medications are metabolised by CYP2C19. All cytochrome enzymes except CYP2D6 are inducible: Binding of an inductor to a transcription factor leads to an increased production of the enzyme after 2-3 weeks. As induction can reduce the efficacy of medication, this delay in the induction effect is of clinical relevance. Inhibitors of cytochrome enzymes are able to remove other substrates from the enzyme or damage the enzyme, which can lead to elevated plasma levels of medication.

As an example, the combination of fluoxetine and amitriptyline is risky and should be avoided in clinical practice. Dr. Döring-Brandl shared a famous case report of a 36-old man who died 6 weeks after being prescribed amitriptyline 150 mg/d and fluoxetine 40 mg/d. The inhibitory effect of fluoxetine on CYP2D6 led to reduced clearance of amitriptyline, resulting in chronic intoxication with the latter.[3] To be on the safe side when prescribing multiple medications, Dr. Döring-Brandl recommends using online drug interaction checking programmes. Table 1 summarises a few medications which should raise red flags upon prescription and prompt to check for any issue with concomitant medication.

"Genetic variation influences inducibility and activity of cytochrome enzymes."

The inducibility and activity of cytochrome enzymes can also be influenced by genetic variation, with the extent of genetic impact and variability differing between the enzymes. In general, genetic variation can lead to different enzyme activity levels, such as ultrarapid, extensive, intermediate, and poor metabolisers. Due to regional differences in the distribution of these genetic factors, it is very important to consider genetic variation in the prescription practice. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetic Working Group provide recommendations on how to deal with information on genetic status.[4,5]

Substance	Effect
Bupropion	Inhibition of CYP2D6
Fluoxetine	Inhibition of CYP2D6, CYP2C19
Fluvoxamine	Inhibiton of CYP1A2
Paroxetine	Inhibition of CYP2D6, CYP3A4
St John's wort	Potent inductor of CYP enzymes and P-glycoprotein
Carbamazepine	Potent inductor of CYP enzymes and P-glycoprotein
Melperone	Inhibitor of CYP2D6

Table 1: Selected psychotropic medications with high risks for drug-drug interactions[6]

Pharmacodynamic interactions

"Combining SSRIs and NSAIDs increases the risk for upper gastrointestinal bleeding."

In addition to pharmacokinetics, pharmacodynamics are also important in terms of drug-drug interactions leading to potentially harmful side effects in polypharmacy. From the wide field of pharmacodynamic interactions, Dr. Döring-Brandl provided a few examples of important interactions that should be considered in psychiatric treatment. Patients concurrently taking selective serotonin reuptake inhibitors (SSRI) and nonsteroidal anti-inflammatory drugs (NSAIDs) or direct oral anticoagulants (DOACs) on a regulars basis are at risk of upper gastrointestinal bleeding since both agents inhibit the transport of serotonin in platelets.[7,8] While many psychiatric medications have a risk of QTc-elongation, it is particularly high for amitriptyline, intravenous haloperidol, methadone, amiodarone, and verapamil.[2] If a patient requires several medications, Dr. Döring-Brandl advises to avoid combining high-risk medications with each other in order to avert future risk of arrhythmias. When combining medications with a risk for QTc elongation, she strongly advises to repeat ECG controls in shorter intervals. Immediate action is required in case of changes in the QTc times, i.e. the patient should be switched to a medication with a lower risk for these QTc elongations. Combining certain medications may increase the risk to develop a serotonin syndrome. Combinations that should be avoided include SSRI/serotonin-norepinephrine reuptake inhibitors and triptane, SSRI and monoamine oxidase (MAO)-inhibitors, 3,4-methylenedioxymethamphetamine (MDMA) and SSRI, cocaine and SSRI as well as tramadol and SSRI.

Drug interactions involving ADHD medication

"The combination of methylphenidate with MAO-inhibitors is contraindicated."

In the treatment of ADHD, certain commonly prescribed medications require particular caution due to a high potential for drug-drug interactions at both the pharmacodynamic and pharmacokinetic levels (see Table 2). Methylphenidate, which is minimally metabolized by cytochrome P450 enzymes, is associated with relatively few high-risk interactions. However, one of the most dangerous and contraindicated combinations is with monoamine oxidase inhibitors (MAOIs), as this may slightly increase the risk of serotonin syndrome.

Medication	Metabolisation	Substances with drug-drug interactions	
		Pharmacodynamic	**Pharmacokinetic**
Methylphenidate	Mainly by carboxylesterase, small portion (5-10%) by CYP2D6	• Alcohol • Tricyclics, guanethidine, amantadine, anti-convulsants • Bupropion • **MAO-inhibitors (!)** • Risperidone[10] • Dopaminergic drugs/ antipsychotics:	• Carbamazepine • Antacids
Amphetamine	CYP2D6 (D-amphetamine)	• MAO-inhibitors, SSRI • Antipsychotics • dopamine agonists, bupropion and L-Dopa • Antihypertensive drugs • Lithium, tricyclics, ethanol • Pain killers	• CYP2D6-inhibitors (e. g. fluoxetine) • If co-medication with SSRI cannot be avoided, the SSRI should not be a CYP2D6 inhibitor
Atomoxetine	CYP2D6 and CYP2C19	• Other drugs with influence on QTc-time • Antihypertensive drugs • Salbutamol and other beta 2-agonists	• CYP2D6-inhibitors (e. g. fluoxetine)
Bupropion*	Mainly by CYP2B6; strong CYP2D6 inhibitor	• MAO-inhibitors • Dopaminergic drugs • Antipsychotics, antidepressants, theophylline and others • Alcohol	• **Tamoxifen** (never combine!) • All CYP2D6 substrates
Guanfacine	CYP3A4 and CYP3A5	• Tricyclics • Mirtazapine • Antipsychotics • Alcohol • Antihypertensive drugs	• CYP3A4/CYP3A5-inhibitors/inductors • Valproic acid
Viloxazine*	Strong CYP1A2-inhibitor; weak inhibitor of CYP2D6 and CYP3A4	• Clozapine	
Clonidine hydrochloride*	Mainly by CYP2D6	• Alcohol, barbiturates, benzodiazepines, opioids • Tricyclics • Beta blockers, digitalis • Antihypertensive medications	• CYP2D6 inhibitors

Table 2: ADHD medications and potential drug-drug interactions[9].

MAO, monoamine oxidase; MPH, methylphenidate; SSRI, selective serotonin reuptake inhibitor
*Approved in USA only

Self-medication and illegal drugs

Intake of OTC medication is common, but often not actively reported. In particular, St. John's wort can raise problems, as it induces most cytochrome enzymes, thus reducing the efficacy of other medications that are substrates of cytochrome enzymes. For instance, there are several case reports of reduced efficacy of methylphenidate when combined with St. John's wort.[11,12] Substance use disorders (SUD) and ADHD frequently co-occur, especially when there are other comorbidities. Most recent guidelines recommend treating SUD and ADHD sufficiently at the same time.[13] Since alcohol can increase the plasma concentration of methylphenidate, patients should abstain from alcohol while they receive treatment with methylphenidate or other stimulants.[14]

Q&A

During the presentation audience members had the opportunity to ask questions via the chat function.

What is the risk for energy drinks to interact with central stimulants and influence efficacy or side effects?

Eva Döring-Brandl: It's known that energy drinks, when consumed extensively, can show clinical interactions by increasing restlessness and at least the subjective effect of the stimulant medication, and also of non-stimulant medication. Some patients with ADHD consume energy drinks as a type of self-medication. The interaction is not well analysed yet.

Do you test the cytochrome status before starting a psychoactive medication, or do you test it only if side effects occur?

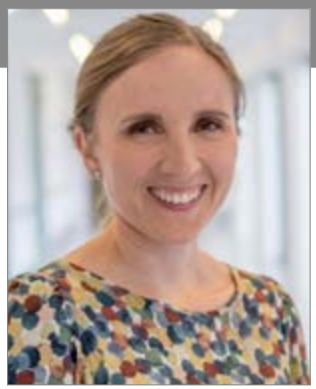
Eva Döring-Brandl: Unfortunately, this type of genetic testing is not covered by the public health insurance in Germany. Consequently, it's not recommended to do cytochrome testing prior to prescription. In cases where you see repeated non-response to different types of medication, or if you experience some very unusual side effects, or if you measure very unusual plasma levels, the standard guidelines recommend genetic testing.

Can you explain how amphetamines and methylphenidate lead to hypertensive crisis when taken with beta blockers? Can this happen when a beta blocker is prescribed in low dose for anxiety?

Eva Döring-Brandl: The antagonising effect of the amphetamines mainly increases the blood pressure by lowering the efficacy of the beta blocker. If the beta blocker is mostly prescribed for anxiety* at low dose and not for the blood pressure itself, this will probably rather not be the main issue when combining these two medications.

*Beta blockers are not approved for anxiety disorders (off-label).

ABOUT THE EXPERT



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EXPERT ADVICE AND RESOURCES

- **Flockhart table** (a comprehensive listing of drug interactions involving the human cytochrome P450 system): https://medicine.iu.edu/internal-medicine/specialties/clinical-pharmacology/drug-interaction-flockhart-table (also available as app for mobile phones)
- **mediQ and Psiac** (online tools for risk assessments of polypharmacy, German)
- **Review on drug-drug interactions with methylphenidate** (Nevels RM et al. German Journal of Psychiatry 2013;16:29-42)
- **Review on clinically significant drug-drug interactions in ADHD** (Schoretsanitis G et al. CNS Drugs. 2019;33(12):1201-22)

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