Psychiatric Drugs and Antibiotics. When Two Worlds Collide

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Abstract

Background: Both psychotropic medication and antibiotic therapy are extensively prescribed. In many cases, these medications are concurrent and the necessity to analyze this particular drug interaction appears.

Aims: To identify in specialized medical databases what these interactions are, which is their biochemical substrate, and which is the optimal method to avoid unwanted drug associations.

Method: Abstracts of PubMed database were automatically filtered using a specific search tool, the keyword data being drug interactions psychotropics, antibiotics and their synonyms, and websites dedicated to drug interactions were interrogated on the same subject.

Results and Discussion: Given that there is not enough clear data, especially for new developed medicines, it seems that drug interactions between antibiotics and psychotropic drugs are generally benign. Even if specialized web applications to identify drug interactions already exist, their results often differ or are not consistent.

Conclusion: Although interactions between psychotropic and antibiotic drugs appear to be generally benign, more valid data are needed to properly assess their impact on treatment efficiency and the patient's quality of life. Antibiotics must be prescribed when necessary and it is advisable to avoid antibiotic classes with the most documented drug interactions: Fluoroquinolones, Macrolides and Anti-tuberculosis drugs.

Keywords: Psychiatric Drugs; Antibiotics; Drug Interactions.

1. Introduction

There is a plethora of data in the literature that supports the idea of a pandemic of psychiatric affections.

Results of the systematic review and meta-analysis indicated that approximately one in five persons experienced a common mental disorder within a 12-month period across general population surveys undertaken in 59 countries. The aggregate lifetime prevalence of common mental disorder was estimated at 29.2% from 85 surveys undertaken across 39 countries (Steel et. al., 2014).

Accordingly, the consumption of psychotropic drugs is at a high level, 1 of 6 US adults reported taking psychiatric drugs at least once (Moore & Mattison, 2017).

Antibiotics are the second most commonly prescribed class of medication in the United States. An awareness and understanding of their potential effects on the central nervous system and their interactions with psychotropic agents is important in the evaluation of neuropsychiatric signs and symptoms in patients (Sternbach & State, 1997). Global antibiotic consumption had increased by 65% from 2000 to 2015 (Klein et. al., 2018; Duceac et. al., 2018).

Because, on the one hand, psychiatric pathology is particularly frequent, often requiring chronic medication, and, on the other hand, infectious pathology is also very common, antibiotics being the second most prescribed medication, the situations in which the two therapeutic classes are also very frequent.

In literature, an increasing prevalence of bacterial infections have been described for patients with psychiatric disorders (Wang et. al., 2014).

Moreover, infections have been associated with increased risks for mental disorders, such as schizophrenia and depression, and recent studies provide evidence for the involvement of infections and the immune system in the etiology of a wide range of mental disorders in children and adolescents (Köhler-Forsberg et. al., 2019; Trandafir et. al., 2018).

Classically, drug interaction refers to the concomitant administration of at least two drugs resulting in different effects compared to the situation in which the drugs would be administered individually (Ciubara et. al., 2018).

From the point of view of interaction mechanisms, we can differentiate pharmacokinetic interactions, such as changes in absorption, distribution, metabolism and excretion, and pharmacodynamic interactions, as with concomitant administration of agonist or antagonist substances for the same receptor.

In medical practice three situations can arise in the drug interaction situation: potentiation of effects (agonist, synergistic effect), reduction of effects (antagonistic effect) or appearance of new, unwanted effects.

Knowing drug interactions is particularly important in practice. Synergistic effects can be used to maximize the desired therapeutic effects, but caution should be taken to avoid overdosing.

Antagonist interaction should also be known to avoid combinations of drugs that decrease each other's effects to a limit that makes them ineffective.

In the particular case of the interaction between psychotropic and antibiotics medications, precautions should be taken to avoid situations where antibiotics become ineffective, not controlling the infection, or where psychiatric medication leads to exacerbations of pathology or withdrawal phenomena.

As a general rule, drug interactions should be avoided, or where this is difficult or impossible, doses should be adjusted accordingly.

Most drug interactions take place at the metabolic stage, of particular importance being the cytochrome P450. Almost all psychotropic drugs are metabolized at this level. Of the various families that are present in human beings, the most interesting in this respect are the 1, 2 and 3, and the most important enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The majority of the enzymes are also involved in the metabolism of endogenous substances, such as steroids or sex hormones, which is also important should there be interference with these substances. As a result of these interactions, the function of the enzymes can either be stimulated (enzyme induction) or inhibited (enzyme inhibition) (Normann et. al., 1998).

2. Methods

Information on "drug interactions" is spread over nearly 300,000 PubMed results. To select relevant articles, a specific search tool was used, with keyword data being: drug interactions psychotropics, antibiotics and their synonyms. The abstracts were manually screened for relevant information and the results regarding psychotropic and antibiotics drugs interactions were summarized in a table. Additionally, websites dedicated to drug interactions were interrogated on the same subject and the results were compared with the previous findings and added to the table.

3. Results

Drug interactions between psychiatric medication and antibiotics appear to have only rare significant clinical consequences, usually benign or under-investigated. There may be more subtle interactions that seem to be underestimated or ignored.

The antibiotics classes most commonly involved in interactions with psychotropic medication are Fluoroquinolones, Macrolides and Anti-tuberculosis drugs.

The most common interactions are those of the antagonist type in which the effect of both classes of medication is reduced, and the the QT interval is prolonged. The most frequent underlying mechanism seems to be the inhibition of cytochrome P450 enzymes.

Drug interactions are reported between antibiotics and typical and atypical antipsychotics, antidepressants from all the classes, selective serotonin reuptake inhibitors, Monoamine oxidase inhibitors, Tricyclics, and Serotonin norepinephrine reuptake inhibitors, Antianxiety/antipanic medications, Stimulants, Mood stabilizers.

There are more adverse drug interactions reported for medicines that are used in practice for a long time, and very few or none for new developed drugs. Even in cases where class membership, structure, or mechanism of action justifies the suspicion of drug interactions, at least theoretically, the data is inconsistent or lacking.

Because interactions are not always clinically evident, their effects are often attributed to other causes and frequently clinicians fail to recognize and report them, so there is no clear epidemiological data on their incidence.

There is a lot of inconsistent or contradictory data on drug interactions in both PubMed literature and on web sites that provide information about drug interactions.

Table 1. Interactions between psychiatric drugs and antibiotics classes

Psychotropics \ Antibiotics			Penicillins	Cephalosporins	Fluoroquinolones	Aminoglycosides	Monobactams	Carbapenems	Macrolides	Glycopeptide	Sulfonamides	Lincomycins	Antituberculosis	Tetracyclines	Polypeptides	Other
Antipsychotics	Typical	Chlorpromazine							⇧							
		Perphenazine							⇩							
		Trifluoperazine			**q**				**q**							
		Mesoridazine														
		Fluphenazine			**q**											
		Thiothixene														
		Molindone														
		Thioridazine			**q**											
		Loxapine														
		Haloperidol											⇩			
	At	Aripiprazole											⇩			

		Clozapine			⇩				⇩				⇩			
		Ziprasidone			⇩				⇩							
		Risperidone			⇩											
		Quetiapine									⇩		⇩			
		Olanzapine			⇩				⇩							
Antidepressants	SSRIs	Citalopram							⇩							
		Escitalopram							⇩							
		Fluvoxamine														
		Paroxetine														
		Fluoxetine														
		Sertraline			**q**				⇧**q**				⇩			
	MAOIs	Selegiline														
		Isocarboxazid														
		Phenelzine														
		Tranylcypromine														
	TCAs	Clomipramine			⇩				**q**							
		Amoxapine			⇩											
		Amitriptyline			⇩											
		Desipramine														
		Nortriptyline			⇩				**q**							
		Doxepin			⇩				**q**							
		Trimipramine			⇩				**q**							
		Imipramine														
		Protiptyline														
	SNRI	Desvenlafaxine														
		Venlafaxine			**q**				**q**							
		Duloxetine			⇩											
Antianxy/antipanic		Lorazepam			⇩								⇩			
		Buspirone														
		Propranolol														
		Clonazepam			⇩								⇩			
		Chlordiazepoxide														
		Oxazepam			⇩								⇩			
		Atenolol														
		Clorazepate														
		Diazepam			⇩								⇩			
		Alprazolam			⇩								⇩			
Stimu		(D)amphetamine	⇩											⇩		
		Methylphenidate														
Mood		Lamotrygine							⇩				⇩			
		Lithium												⇧		

References given in parentheses: “Antianx” - Antianxiety/antipanic medications, “Sti” - Stimulants, “M” - Mood stabilizers, “SSRIs” - Selective serotonin reuptake inhibitors, “MAOIs” - Monoamine oxidase inhibitors, “TCAs” - Tricyclics, “SNRI” - Seretonin norepinephrine reuptake inhibitors, “q” - prolongation of the QT interval

4. Discussion

A significant number of new psychotropic drugs are introduced every year. Although not as frequently, antibiotic classes and derivatives also appear. New drugs and drugs with a narrow therapeutic area are most likely to cause serious negative drug interactions.

In the process of developing a new drug, it is impossible to study in vivo interactions with all other drugs. Possible drug interactions can sometimes be estimated by looking at the theoretical models of action of the drug at the carrier and the receptor levels, most frequently being analyzed at the level of the cytochrome P450 enzyme assembly. This theoretical analysis is complicated by the fact that in humans there are 5 isoenzymes involved in this process that can be modulated differently from a large number of drugs and the clinical expression of these interactions is difficult to predict (Straticiuc et. al., 2016).

A logical way to prevent potential drug interactions for a new drug would be to test interactions at least for the most common association, which is also the case for antibiotics and psychiatric drugs.

Another way in which drug interactions between anti-infectious therapy and psychotropic medication are discovered is the publication of articles describing clinical cases of interactions. These are usually case studies that describe well-documented clinical effects, for example lithium intoxication reported in the case of a patient who was concomitantly treated with tetracycline. These findings are strained by the fact that they are based on a small number of cases where the genotype, phenotype, or other specific, individual factors can influence the outcome. Sometimes these results are not reproducible to another patient or animal study.

Beyond the classic drug interactions, antibiotics and psychotropic drugs, psychiatric pathology implicitly, seem to be linked by a particular mechanism. Recent studies identify links between intestinal dysbiosis, commonly caused by broad spectrum antibiotics, and psychiatric pathology, especially schizophrenia and depression. This phenomenon seems to be based on the gut-brain axis biochemical signaling from the gastrointestinal tract to the central nervous system (Zhu et. al., 2017; Ciubotaru et. al., 2016; "Drug Interactions Checker - For Drugs, Food & Alcohol", 2019; Drug Interaction Checker, 2019; Drug Interaction Checker | UCLA Health Library, Los Angeles, CA, 2019).

Recognizing drug interactions based on memory is a burden for physicians. To summarize treatments from diverse therapeutic areas is even more difficult for family doctors. The only viable solution is to turn to specialized databases to identify drug interactions.

None of the web sites analyzed seems to offer the clinician the perfect solution to ensure the absence of drug interactions. In some cases, the number of drug interactions is exaggerated, probably by considering theoretical interaction mechanisms without quantifying the actual impact on the effectiveness of therapy. In other cases, for interactions documented through clinical trials, the response to the site query is null.

A desirable solution would be to implement, in the existing medical software used by clinicians, a module that automatically provides 3-level warnings, caution, moderate or mildrisk on possible drug interactions when writing an electronic prescription.

5. Conclusions

Although interactions between psychotropic and antibiotic drugs appear to be generally benign, more valid data is needed to properly assess their impact on treatment efficiency and patient's quality of life.

Antibiotics must be prescribed for patients receiving concomitant psychiatric treatment only when necessary.

When possible, it is advisable to avoid antibiotic classes with the most documented drug interactions, such as Fluoroquinolones, Macrolides and Anti-tuberculosis drugs, and to analyze any possible drug interaction using updated software applications.

When the association is absolutely necessary, the therapeutic response should be carefully monitored, routine electrocardiographic testing for prolonged QT interval must be done and the dosages should be adjusted accordingly.

Conflicts of Interest

The authors declare no conflict of interest.

References

Ciubara, A.B., Nechita, A., Tudor, R.C., Matei, M., Tutunaru, D., Sirbu, P.D. (2018). Social and Medical Ethics: Implications for Romanian Protocols Regarding the Therapy of Alcohol Withdrawal Syndrome in Trauma Patients. Revista de Cercetare si Interventie Sociala, 60, 174-179.

Drug Interaction Checker | UCLA Health Library, Los Angeles, CA. (2019). Retrieved from http://healthinfo.uclahealth.org/Library/DrugReference/DrugInteraction/

Drug Interaction Checker. (2019). Retrieved from https://reference.medscape.com/drug-interactionchecker

Drug Interactions Checker - For Drugs, Food & Alcohol. (2019). Retrieved from https://www.drugs.com/drug_interactions.html

Duceac, L.-D., Stafie, L., Valeanu, I., Mitrea, G., Baciu, G., Banu, E.-A., Romila, L., Luca, A.-C. (2018). Sepsis in paediatrics – a special form of infection associated to medical assistance. International Journal Of Medical Dentistry, 22(3), 229-235.

Filip-Ciubotaru, Florina-Mihaela & Manciuc, Carmen & Stoleriu, Gabriela & Foia, Liliana. (2016). NADPH Oxidase: Structure And Activation Mechanisms (Review). Note I. 120. 29-33.

Klein, E., Van Boeckel, T., Martinez, E., Pant, S., Gandra, S., & Levin, S. et. al. (2018). Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proceedings Of The National Academy Of Sciences, 115(15), E3463-E3470. doi: 10.1073/pnas.1717295115

Köhler-Forsberg, O., Petersen, L., Gasse, C., Mortensen, P., Dalsgaard, S., & Yolken, R. et. al. (2019). A Nationwide Study in Denmark of the Association Between Treated Infections and the Subsequent Risk of Treated Mental Disorders in Children and Adolescents. JAMA Psychiatry, 76(3), 271. doi: 10.1001/jamapsychiatry.2018.3428

Moore, T., & Mattison, D. (2017). Adult Utilization of Psychiatric Drugs and Differences by Sex, Age, and Race. JAMA Internal Medicine, 177(2), 274. doi: 10.1001/jamainternmed.2016.7507.

Normann, Claus & Hesslinger, B & Bauer, Joachim & Berger, M & Walden, Joy. (1998). Significance of hepatic cytochrome P450 enzymes for psychopharmacology. Der Nervenarzt. 69. 944-55.

Steel, Z., Marnane, C., Iranpour, C., Chey, T., Jackson, J., Patel, V., & Silove, D. (2014). The global prevalence of common mental disorders: a systematic review and meta-analysis 1980–2013. International Journal Of Epidemiology, 43(2), 476-493. doi: 10.1093/ije/dyu038.

Sternbach, H., & State, R. (1997). Antibiotics: Neuropsychiatric Effects and Psychotropic Interactions. Harvard Review Of Psychiatry, 5(4), 214-226. doi: 10.3109/10673229709000304.

Straticiuc, S., Ignat, A., Hanganu, E., Lupu, V., Ciubara, A., & Cretu, R. (2016). Neisseria meningitidis Serogroup C Causing Primary Arthritis in a Child. Medicine, 95(5), e2745. doi: 10.1097/md.0000000000002745.

Trandafir, Laura & Baciu, G & Constantin, Maria-Magdalena & Maștaleru, Alexandra & oana-raluca, Temneanu & Mihai, B & Novac, O & Frasinariu, O.E. & Ivan, A & Tudorachi, N.B. & Hiary, R.A.L. & Moscalu, Mihaela. (2018). Predictive biological markers in post-therapeutic evolution in obese patients. Revista de Chimie. 69. 3048-3051.

Wang, X., Zhang, L., Lei, Y., Liu, X., Zhou, X., & Liu, Y. et. al. (2014). Meta-Analysis of Infectious Agents and Depression. Scientific Reports, 4(1). doi: 10.1038/srep04530

Zhu, X., Han, Y., Du, J., Liu, R., Jin, K., & Yi, W. (2017). Microbiota-gut-brain axis and the central nervous system. Oncotarget, 8(32). doi: 10.18632/oncotarget.17754.