International Journal of Cardiology 219 (2016) 367–372

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Cardiovascular side effects of psychopharmacologic therapy

Ines Potočnjak [a,*], Vesna Degoricija [b,a], Dina Vukičević Baudoin [a], Josip Čulig [c,d], Miro Jakovljević [b,e]

[a] University Hospital Center Sisters of Charity, Vinogradska cesta 29, 10000 Zagreb, Croatia
[b] University of Zagreb School of Medicine, Šalata 3, 10000 Zagreb, Croatia
[c] Department of Pharmacoepidemiology, Andrija Štampar Teaching Institute of Public Health, Mirogojska 16, 10000 Zagreb, Croatia
[d] Department of Pharmacology, School of Medicine, Josip Juraj Strossmayer University Osijek, J. Huttlera 4, 31000 Osijek, Croatia
[e] Department of Psychiatry, University Hospital Centre Zagreb, Kišpatićeva 12, 10000 Zagreb, Croatia

ARTICLE INFO

Article history:
Received 18 April 2016
Accepted 18 June 2016
Available online 20 June 2016

Keywords:
Psychopharmacology
Psychotropic drugs
Pharmacotherapy
Cardiovascular system
Side effects

ABSTRACT

WHO defined in 1976 psychopharmaca as drugs affecting psychological functions, behaviour and self-perception. Psychopharmacology is the study of pharmacological agents that affect mental and emotional functions. Creative approach to psychopharmacotherapy reflects a transdisciplinary, integrative and person-centered psychiatry. Psychiatric disorders often occur in cardiac patients and can affect the clinical presentation and morbidity. Cardiovascular (CV) side effects (SE) caused by psychopharmaceutic agents require comprehensive attention. Therapeutic approach can increase placebo and decrease nocebo reactions. The main purpose of this review is to comprehend CV SE of psychotropic drugs (PD).

Critical overview of CV SE of PD will be presented in this review. Search was directed but not limited to CV effects of psychopharmacological substances, namely antipsychotics, anxiolytics, hypnotics, sedatives, antidepressants and stimulants. Literature review was performed and data identified by searches of Medline and PubMed for period from 2004 to 2015. Only full articles and abstracts published in English were included.

SE of PD are organized according to the following types of CV effects: cardiac and circulatory effects, abnormalities of cardiac repolarisation and arrhythmias and heart muscle disease. There is wide spectrum and various CV effects of PD. Results of this review are based on literature research. The reviewed data came largely from prevalence studies, case reports, and cross-sectional studies.

Psychopharmacotherapy of psychiatric disorders is complex and when concomitantly present with CV disease, presentation of drug SEs can significantly contribute to illness course. Further development of creative psychopharmacotherapy is required to deal with CV effects of PD.

1. Introduction

This paper discusses cardiovascular side effects of psychopharmacotherapy. In the first part of this article overview of classification, commonly used psychotropic drugs, cardiovascular side effects and general data of cardiovascular effects are given. The second part deals with the cardiovascular side effects of psychopharmacs divided in groups as follows cardiac and circulatory effects, abnormalities of cardiac repolarisation and arrhythmias and heart muscle disease are described. This paper underlines the importance of cardiovascular effects of psychopharmacologic therapy in order to prevent them.

Prescribing psychotropic drugs (PD) is frequent requirement in clinical practice. According to the definition of The World Health Organization (WHO) from 1976, psychopharmaca are drugs that affect psychological functions, behaviour and self-perception. This chemical compounds in defined dose affect psychological behaviour. Psychopharmaceutic or PD are medications for treatment of psychological disorders. According to The Anatomical Therapeutic Chemical (ATC) Classification System, nervous system drugs are sorted into several groups as shown in Table 1 [1,2]. Medical group N includes anaesthetics, analgesics, hypnotics, anxiolytics, antidepressants, drugs against drug addiction and other drugs to treat diseases of nervous system [3]. PD have various cardiovascular (CV) side effects (SE). Furthermore, polypharmacy is the practice of administering or using multiple medications in the treatment of a single disease or several coexisting conditions. During the therapy it is important to contain pts' active participation. Thorough pt instruction has to be provided and they should be familiar with SE, their prevention, early detection and treatment.

1.1. Commonly used psychotropic drugs

Psychopharmacotherapy is considered as the primary treatment for all serious mental disorders including schizophrenias, bipolar disorders, depressions, anxiety disorders, obsessive–compulsive disorders, etc. [4].

* Corresponding author.
E-mail address: ines.potocnjak@yahoo.com (I. Potočnjak).

http://dx.doi.org/10.1016/j.ijcard.2016.06.057
0167-5273/

The number of the effective medications significantly increased [5]. Positive therapeutic context may significantly increase placebo and decrease nocebo responses [4]. It is known that creative approach to psychopharmacotherapy reflects a synergism in the frame of transdisciplinary holistic, integrative and person-centered psychiatry [4]. Commonly used PD are antipsychotics and antidepressants, comprising of tricyclic anti-depressants (TCAs), selective serotonin and other neurotransmitter re-uptake inhibitors (SSRI and SNRI), mood stabilizers, anxiolytic agents and medications for opioid addiction treatment [6]. Psychiatric medications are associated with a variety of possible adverse effects (AE) [7]. The mechanisms of AE in psychotropic medications might not always be known [7]. Awareness of the mechanisms for adverse drug reactions (ADR) can help to direct prescription choice [7]. ADR can be augmented and bizarre. Augmented ADR are predictable, depending on dose and pharmacological characteristics of the drug. In this paper augmented ADR will be presented. It is important to note that the incidence of mortality is higher among psychiatric pts than in general population [8]. Sudden death (SD) associated with PD is an issue which is currently debated worldwide [9].

Table 1
Classification of psychopharmaceutic agents registered in Republic of Croatia according to ATK system.

N03	Antiepileptics	
N03AA	Barbiturates and derivatives	Methylphenobarbital, phenobarbital, primidone
N03AB	Hydantoin derivatives	Phenytoin
N03AC	Oxazolidine derivatives	Paramethadione
N03AD	Succinimide derivatives	Ethosuximide
N03AE	Benzodiazepine derivatives	Clonazepam
N03AF	Carboxamide derivatives	Carbamazepine
N03AG	Fatty acids derivatives	Valproic acid, valpromide
N03AX	Other antiepileptics	Lamotrigine, topiramate, gabapentin
N05	Psycholeptics	
N05A	Antipsychotics	
N05AA	Phenothiazines with aliphatic side-chain	Levomepromazine, promazine
N05AB	Phenothiazines with piperazine structure	Fluphenazine, perazin
N05AC	Phenothiazines with piperadine structure	Tioridazine
N05AD	Butyrophenone derivatives	Haloperidol
N05AE	Indole derivatives	Ziprasidone
N05AH	Diazepines, oksazepines, thiazepines and oxepines	Clozapine, olanzapine, quetiapine
N05AL	Benzamides	Sulpiride
N05AN	Lithium	Lithium
N05AX	Other antipsychotics	Risperidone
N05B	Anxiolytics	
N05BA	Benzodiazepine derivatives	Alprazolam, bromazepam, diazepam, lorazepam, medazepam, oxazepam
N05BC	Carbamates	Meprobamate
N05C	Hypnotics and sedatives	
N05CD	Benzodiazepine derivatives	Flurazepam, midazolam, nitrazepam
N05CF	Benzodiazepine related drugs	Zolpidem
N05CM	Other hypnotics and sedatives	Valeriane radix
N06	Psychoanaleptics	
N06A	Antidepressants	
N06AA	Non-selective monoamine reuptake inhibitors	Amitriptyline, clomipramine, maprotiline
N06AB	Selective serotonin reuptake inhibitors	Fluvoxamine, fluoxetine, sertraline, paroxetine, escitalopram
N06AG	Monoamine oxidase A inhibitors	Moclobemide
N06AX	Other antidepressants	Tianeptine, reboxetine, venlafaxine
N06B	Psychostimulants, agents used for ADHD and nootropics	
N06BX	Other psychostimulants and nootropics	Piracetam
N06D	Anti-dementia drugs	Donepezil
N06DX	Other anti-dementia drugs	Ginkgo folium

1.2. Cardiovascular side effects

The WHO has defined an ADR as a response to a drug that is noxious and unintended and occurs at average dose in pts for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Drug-related SE and ADR result from the intended use of pharmaceuticals. SE may vary individually, by age, weight, gender, ethnicity, diseases and general health. Further, SE can happen during initiation, decreasing or increasing dosages, or ending a medication treatment. When severe SE occur, medication may be discontinued, the dosage adjusted or a second medication prescribed. Drugs may cause various CV SE, from abnormal heart rate (HR) to heart attack or sudden death. CV disease (CVD) is an extensive class of disorders that involve the heart and the blood vessels [10]. CVDs include following conditions such as angina, atherosclerosis, cerebrovascular disease, coronary artery disease, heart attack, myocarditis, peripheral vascular disease and stroke [10]. CV SEs of antipsychotics and antidepressants are prolonged baseline QTc, myo(peri)carditis, cardiomyopathy, coronary disease and hypertension. The known CV complications of PD and the significant consequences of depression treatment in pts with previous cardiac history was already discussed in literature [10]. In cardiac pts PDs should be restricted because of SE they have on the CV system. They include orthostatic hypotension, tachycardia, reduction in HR variability and slowing of intraventricular conduction [10]. Psychopharmaca which have various CV effects may also harmfully affect clinical outcome of cardiac pts. The published data indicates that pts with severe mental illness should be considered as a 'high risk' population with concern to CV morbidity and mortality [11]. In addition, psychiatric pts are predisposed to abnormalities in cardiac rate, and SD. There is evidence that mortality rate is high in psychiatric pts versus general population [12]. There is an emergent evidence that people affected by psychiatric disorders are more likely to suffer from CV disease [11,13] [14,15,16]. Among modifiable factors that attribute to CV RFs are psychosocial factors [11]. The relative contributions to cardiac risk of specific antipsychotic agents rests to be clarified [14]. Pts must be closely monitored for the CV risks related to psychopharmaceutic agents. A comprehensive risk assessment needs to be applied before initiation of PD treatment to reduce the risk of serious CV SE. The evaluation must include a medical history of HD, present and previous CV symptoms, used medications, assessment of potential drug interactions, and an electrocardiogram (ECG) for assessment of HD signs, conduction disorders, or prolonged QT interval. ECG monitoring includes measure QTc in all pts prescribed antipsychotics. It should be repeated as clinically indicated. Integrated care approach can optimize health outcomes [17]. Special precaution is needed with drugs that may have effects, SEs or interactions [18]. Furthermore, drug consumption is high and many are used chronically [19]. Due to the risk of AE and drug–drug interactions, the prescribing and dosage of should be carefully re-evaluated [19]. Critical judgement and careful drug prescription is compulsory. Regular follow-up and re-evaluation should be performed according to the recommendations. Collaboration with patients may significantly improve treatment outcome [4]. Similarly, a significant increase in dose of these drugs requires re-evaluating symptoms and a new ECG. Drug discontinuation should be performed if necessary. If the psychiatric disease is life threatening, a higher CV risk may be accepted, but it demands close follow-up.

1.3. Data for Croatia

According to the drug consumption in Croatia from 2007 to 2012, drugs that affect the nervous system, N group, are the second highest in total consumption, amounting to 815.6 million kunas in 2012 [3]. The same, second place in consumption and in financial terms, these drugs hold through the entire period from 2007 to 2012 [3]. Total consumption of drugs that act on the nervous system is 794,628,399 [20]. According to the report on the SE of drugs in 2014, by the Agency for Medicinal Products and Medical Devices (HALMED) on monitoring