Epilepsy & Behavior xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Review

Proconvulsant effects of antidepressants — What is the current evidence?

Cecilie Johannessen Landmark [a,b,c,*], Oliver Henning [b], Svein I. Johannessen [b,c]

[a] Dept. of Life Sciences and Health, Programme for Pharmacy, Faculty of Health Science, Oslo and Akershus University College of Applied Sciences, Oslo, Norway
[b] The National Center for Epilepsy, Sandvika, Oslo University Hospital, Oslo, Norway
[c] Department of Pharmacology, Oslo University Hospital, Oslo, Norway

ARTICLE INFO

Article history:
Revised 23 January 2016
Accepted 25 January 2016
Available online xxxx

Keywords:
Antidepressant drugs
Proconvulsant
Seizures
Drug safety

ABSTRACT

Antidepressant drugs may have proconvulsant effects. Psychiatric comorbidity in epilepsy is common. Prescribers might be reluctant to initiate treatment with antidepressants in fear of seizure aggravation. The purpose of this review was to focus upon the current evidence for proconvulsant effects of antidepressants and possible clinical implications. Most antidepressants are regarded as safe and may be used in patients with epilepsy, such as the newer serotonin and/or noradrenaline reuptake inhibitors. Four older drugs should, however, be avoided or used with caution; amoxapine, bupropion, clomipramine and maprotiline. Proconvulsant effects are concentration-related. Optimization of drug treatment includes considerations of pharmacokinetic variability to avoid high serum concentrations of the most proconvulsant antidepressants. The risk of seizures is regarded as small and should, therefore, not hamper the pharmacological treatment of depression in people with epilepsy.

1. Introduction

Antidepressants drugs have been used to treat symptoms of depression since they were introduced in the late 1950s. They consist of a broad range of drugs, all affecting the neurochemical balance of monoamine neurotransmitters in the central nervous system. Some antidepressants have been demonstrated to have proconvulsant effects. In the present review, the main focus will be on patients with epilepsy, since they are most vulnerable to have seizures because of a lower seizure threshold than the population as a whole. Seizures caused by excessive intake of antidepressants or overdose will, however, be briefly described in general. A prevalence rate of depression in epilepsy between 6 and 30% has been shown with various methods [1–5]. Patients with epilepsy and comorbid psychiatric disorders form a large group. Antiepileptic drugs have various beneficial pharmacological effects in psychiatric disorders and are increasingly used in such indications [6–8]. Extensive polypharmacy might lead to interactions and adverse effects [4,9]. Studies have shown that psychiatric disorders in these patients may be underdiagnosed and undertreated [10,11]. A recent survey showed that the main barrier in treating depression in patients with epilepsy is the fear of an increased seizure frequency, according to 52% of primary care physicians, and even 10% of neurologists [12]. Updated knowledge of which antidepressants may have proconvulsant effects and, thus, should be avoided is, therefore, of utmost importance.

The purpose of the present review was to focus upon the current evidence of possible proconvulsant effects of antidepressants and their clinical implications, in order to help prescribers decide which antidepressants should be avoided in patients with epilepsy.

1.1. Description of antidepressants

Antidepressant drugs are defined according to the classification of drugs based upon the Anatomical Therapeutic Chemical classification (ATC)-codes where antiepileptic drugs (AEDs) are defined as N06A [13]. Classification of antidepressants is summarized in Table 1. The main categories include the newer selective serotonin reuptake inhibitors (SSRIs), the older nonselective monoamine reuptake inhibitors or tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, selective or nonselective for MAO_A, and other antidepressants. They also include the newer selective serotonin and noradrenaline reuptake inhibitors (venlafaxine, duloxetine, reboxetine). Their possible propensities to cause proconvulsant effects will be described.

1.2. Search criteria and literature review

The present review is based upon recently published articles identified by searches in PubMed and Google Scholar, in addition to the authors' files. Selected publications of interest were included (1982–2015) with emphasis on the last five years. The search period was to January 2016. Peer-reviewed articles or abstracts on the topic in recognized international journals in English were included, whereas non-English articles were disregarded. Both preclinical and clinical and acute and chronic studies were regarded as relevant, as well as the use of various animal models. Review articles giving a broad and updated overview

* Corresponding author at: Dept. of Life Sciences and Health, Programme for Pharmacy, Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences, Pilestredet 50, N-0167 Oslo, Norway. Tel.: +47 22452360; fax: +47 22452335.
E-mail address: cecilie.landmark@hioa.no (C. Johannessen Landmark).

http://dx.doi.org/10.1016/j.yebeh.2016.01.029
1525-5050/

Table 1
Classification of antidepressants and their propensity to cause seizures.

Antidepressant drug classes	Drug examples	Drugs with propensity to cause seizures and metabolic pathway
Nonselective monoamine reuptake inhibitors (TCA)	Amitriptyline, doxepin, nortriptyline, trimipramine	*Clomipramine* (CYP1A2, 3A4, 2D6)
Selective serotonin reuptake inhibitors (SSRI)	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	*None*
Selective noradrenaline or noradrenaline/serotonin reuptake inhibitors (SNRI)	Venlafaxine, reboxetine, duloxetine	*None*
Monoamine oxidase inhibitors (MAO), nonselective		*Maprotiline* (CYP2D6), *amoxapine* (CYP2D6)
Monoamine oxidase A inhibitors (MAO_A)	Moclobemide	*None*
Other antidepressants	Mianserin, mirtazapine	*Bupropion* (CYP2B6), inhibitor of CYP2D6

The classification of antidepressants is based on the ATC classification system [13].

regarding possible proconvulsant effects of antidepressants were also included. General reviews with a scope besides proconvulsant effects were disregarded. During the searches, the key words antidepressants (specific searches for amoxapine, bupropion, clomipramine, maprotiline, mianserin), anticonvulsant, antiepileptic drugs, clinical study, dose, drug safety, interactions, mice, overdose, preclinical study, proconvulsant, SNRI, SSRI, rat, therapeutic drug monitoring, tricyclic antidepressant, and zebrafish were used, and the various key words were combined.

2. Proconvulsant effects of antidepressants

2.1. Neurochemical background

The monoamines are the main neurotransmitters that are affected by antidepressants. It is well known that it takes several weeks to observe clinical effects of these drugs, pointing to a long-term change in establishing a neurochemical balance within these neuronal networks. The main targets for pharmacological action of antidepressants vs AEDs in the synapses are shown in Fig. 1. Antidepressants may disturb the neuronal balance and control of excitability, leading to seizures. Seizures may occur as a consequence of a misbalance between inhibitory GABAergic and excitatory glutamatergic neurotransmission with increase in glutamatergic activation and, thus, excessive calcium influx, initiating intracellular processes. The underlying mechanisms are not clear [14]. In a recent review, the role of serotonin in the control of neuronal excitability, epileptogenesis, and seizure propagation is emphasized, and various effects are observed through modulation of different subtypes of 5-HT receptors throughout the brain [15]. Noradrenergic and serotonergic effects of antidepressants seem to be anticonvulsant in therapeutic doses, whereas supratherapeutic doses or serum concentrations may activate other neurochemical pathways that may culminate in seizures [16–18].

2.2. Preclinical evidence of specific drugs

When reviewing the literature, four antidepressants, in particular, appear to have most pronounced proconvulsant effects, namely the tricyclic antidepressant clomipramine, the unselective MAO-inhibitors amoxapine and maprotiline, and the atypical antidepressant bupropion, the latter being a noradrenaline and dopamine reuptake inhibitor (Table 1). For all other antidepressants, the seizure risk is regarded as low.

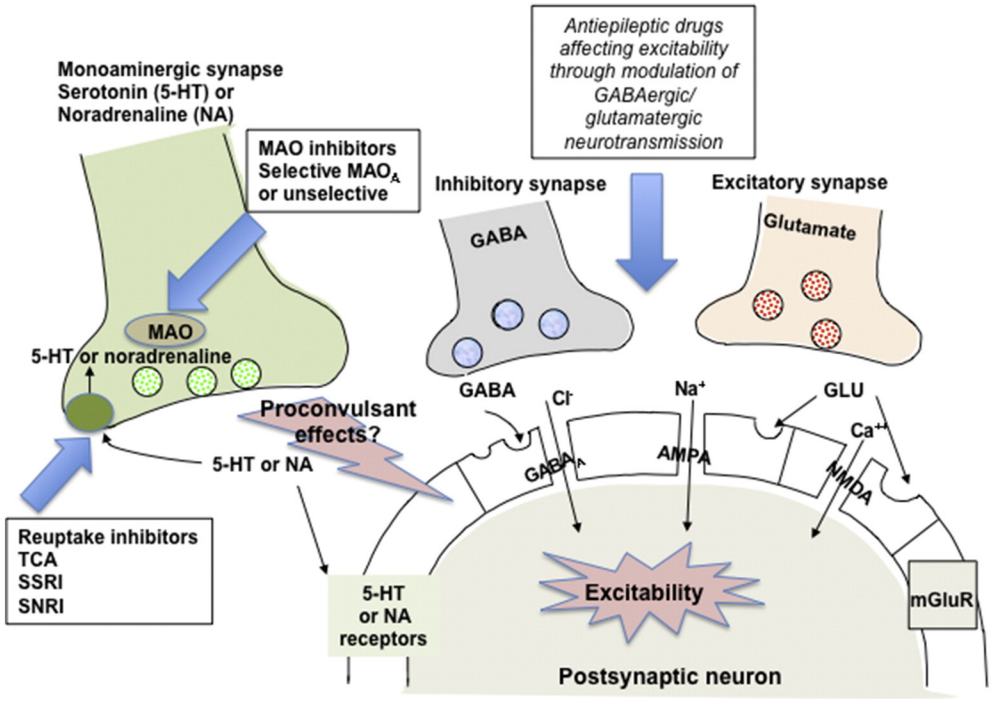

Fig. 1. Mechanisms of action of antidepressants vs antiepileptic drugs in the synapses.

Please cite this article as: Johannessen Landmark C, et al, Proconvulsant effects of antidepressants — What is the current evidence? Epilepsy Behav (2016), http://dx.doi.org/10.1016/j.yebeh.2016.01.029