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Off-label uses of drugs for depression

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ABSTRACT

The prescription of drugs for depression is rising rapidly. One of the reasons for this trend is their many off-label uses. Up to one third of all prescriptions are for non-indicated use, which in addition to drug repurposing includes different dosing or duration than those recommended. In this review, we elaborate on what antidepressants can treat besides depression. The five classes of drugs for depression are introduced, and their mechanisms of action and serious side effects are described. The most common off-label uses of antidepressants are discussed, with a special focus on treating eating disorders, sleep problems, smoking cessation and managing chronic pain. Depression is often a comorbidity when antidepressants are chosen as therapy, but good therapeutic effects have been observed for other conditions also when depression is not involved. Finally, a new type of antidepressant developed from the hallucinogenic "party drug" ketamine is briefly introduced. This recent development suggests that antidepressants will keep playing a central role in medicine for years to come.

1. Introduction

The use of drugs for depression has increased significantly in western countries including the UK (Iacobucci, 2019), Canada (Hemels et al., 2002), USA (National Center for Health Statistics, 2014) and other members of the Organization for Economic Cooperation and Development (OECD) (Fig. 1). The United States was not included in the OECD analysis, but with 11% of Americans over the age of 12 taking antidepressants (Pratt et al., 2011), they would be on the top of the chart together with Iceland. There are several possible explanations for the increase in antidepressant consumption. As suggested by the OECD, the current treatment regime lasts longer than what was common in the past. Secondly, antidepressants are now prescribed not only for severe depression, but also for mild depression, anxiety, and social phobia. Another plausible explanation is the many off-label uses for certain antidepressants (Stone et al., 2003; Wong et al., 2017). The global market of drugs for depression is estimated to be worth $13 billion (Medgadget, 2019) and, as recent studies in Canada revealed, nearly one third (29%) of all antidepressants are prescribed for an off-label indication (Wong et al., 2016, 2017). This clearly shows the large scale of off-label uses of drugs for depression.

Off-label use can mean repurposing of the drug. It can also mean an atypical use of a drug, such as use of a different dosage, duration of use, dosing frequency, use of a different method of administration (e.g. orally instead of intravenously), or use by a different patient group (e.g. children instead of adults). Pharmaceutical companies are not allowed to promote a drug for a use that is not approved by the appropriate agency such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). However, it is legal to inform about studies that show positive results in off-label applications, and it is also legal for a physician to prescribe a medication for off-label use.

Regulations dealing with off-label drug use vary in different countries. For example, in Spain prescription of medicines off-label must be exceptional, limited to situations where there is no authorized alternative for the patient and subject to his/her consent. In Netherlands, off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use. In the UK, drug prescribers are given guidance from the General Medical Council (Health Action International, 2018; STAMP Commission Expert Group, 2017). Such regulations are created to protect patients from ineffective and unsafe drugs, or therapies in which there is little or no evidence to support their use. Secondly, they should encourage pharmaceutical companies to move from "off-label" to "on-label" by applying for marketing authorization. Here, we use the term off-label to refer to repurposing of the drug.

In this review we shortly describe how different classes of antidepressants work, discuss their most common off-label applications and potential hazards related with their use.

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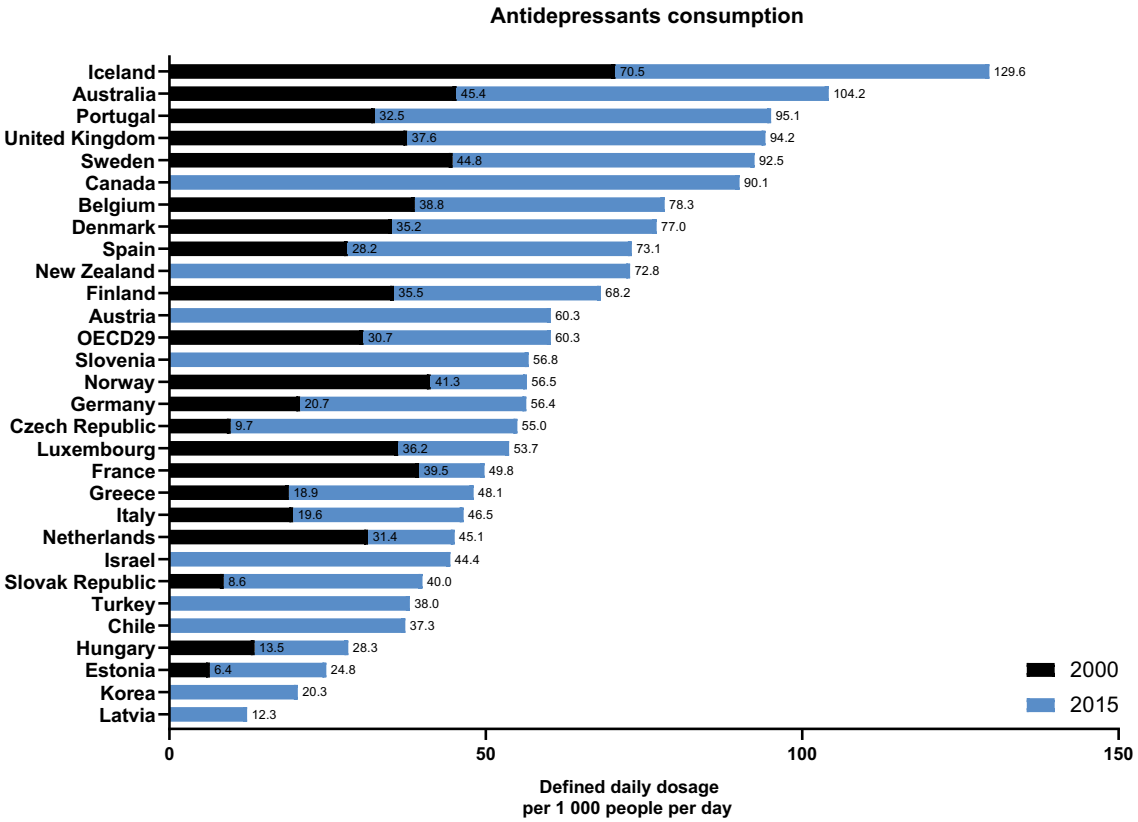

Fig. 1. Consumption of drugs for depression in OECD countries in 2000 and 2015. Source: OECD Health Statistics (2017), (OECD, 2017).

2. Classification of drugs for depression

Antidepressants are designed to treat depression and therefore target pathways in the brain that regulate the mood. Three monoamines, which primarily function as neurotransmitters, are believed to be involved in this process. Serotonin regulates mood, appetite, sleep, memory, social behavior and sexual desire. Norepinephrine influences alertness and motor function and helps regulate blood pressure and heart rate in response to stress. Finally, dopamine is important for decision-making, motivation, arousal and the signaling of pleasure and reward. In people suffering from depression, these neurotransmitters show reduced availability in the brain. There are five major classes of antidepressants (Table 1), and they act by increasing the level of one or more of these neurotransmitters (Hillhouse and Porter, 2015) (Fig. 2). The most commonly prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). These drugs inhibit the reabsorption of serotonin and/or norepinephrine in the brain. Tricyclic antidepressants (TCAs), on the other hand, block absorption of serotonin and norepinephrine, as well as acetylcholine, into nerve cells. The fourth class of antidepressants, monoamine oxidase inhibitors (MAOIs), inhibits the action of monoamine oxidase which breaks down monoamines. Finally, the class of atypical antidepressants changes the levels of one or more neurotransmitters, such as dopamine, serotonin or norepinephrine by various mechanisms (Table 1). With the exception of MAOIs, all classes of antidepressants have several off-label uses (Table 2). Some of these uses are discussed in the following sections.

2.1. Role of antidepressants in the treatment of eating disorders

Eating disorders are characterized by abnormal eating behavior which negatively affects the dietary intake as well as physical and mental health of the affected person. Three primary eating disorders are recognized: anorexia nervosa, bulimia nervosa, and binge eating disorder (American Psychiatric Association, 2013). All are serious psychiatric disorders, and common comorbidities include depression, anxiety and obsessive-compulsive behavior (Amodeo et al., 2019; Marvanova and Gramith, 2018). The main criteria for being diagnosed with anorexia nervosa are a significantly low body weight, an intense fear of weight gain, and a disturbed body perception (American Psychiatric Association, 2013). Diagnostic criteria for bulimia nervosa include recurrent binges (over-eating associated with loss of control) and inappropriate compensatory behavior such as vomiting, excessive physical activity or fasting (American Psychiatric Association, 2013). Binge eating disorder is the most common eating disorder and is characterized by binge eating without use of the extreme compensatory strategies seen in bulimia nervosa (American Psychiatric Association, 2013). Binge eating disorder is frequently associated with obesity, and is under-diagnosed and under-treated (Amodeo et al., 2019). As eating disorders have the highest mortality rate of all mental health disorders, improved treatment is warranted (Gibson et al., 2019).

Since patients with eating disorders suffer from many of the same symptoms as the mentally ill, antipsychotic drugs including chlorpromazine (Delay and Deniker, 1955) and the antidepressant imipramine (Table 2) (Kuhn, 1958; Steinberg and Himmerich, 2012) were also tested in this patient group (Johnson et al., 1983; Yellowlees, 1985). However, these early studies were inconclusive with regards to benefit (Himmerich and Treasure, 2018). In 1986, the SSRI fluoxetine (Table 2) was marketed. The new drug was tested in a small study on patients with bulimia nervosa with positive results (Freeman and Hampson, 1987). Fluoxetine was approved by the FDA in 1987 and is now the first-line psychopharmacological treatment for bulimia nervosa (Aigner et al., 2011).

The observed efficacy of antidepressants as treatment for bulimia nervosa led to trials to evaluate their effect on binge eating disorder. Antidepressants that have shown promising results include bupropion,

Table 1
Classes, mechanisms of action and side effects of drugs for depression[a].

Class (*traditional terminology*[b])	Pharmacology	Mechanism of action	*Drugs (trade names)*	Side effects
Selective Serotonin Reuptake Inhibitors (SSRI)	Serotonin	reuptake inhibitors (SERT)	Citalopram (Celexa, Cipramil) Escitalopram (Lexapro, Cipralex) Fluoxetine (Prozac, Sarafem, Adofen) Fluvoxamine (Luvox, Faverin, Fluvoxin)[c] Paroxetine (Paxil, Pexeva) Sertraline (Zoloft)	Nausea, insomnia, nervousness, tremors, sexual dysfunction, fatigue, weight gain, anxiety, drowsiness, dry mouth, diarrhea, dizziness, blurred vision
		reuptake inhibitor (SERT), receptor partial agonist (5-HT1A)	Vilazodone (Viibryd)	
		reuptake inhibitor (SERT), receptor partial agonist (5-HT1A), receptor antagonist (5-HT3)	Vortioxetine (Trintellix, Brintellix)	
Serotonin and Norepinephrine Uptake Inhibitors (SNRI)	Serotonin, norepinephrine	reuptake inhibitors (SERT and NET)	Desvenlafaxine (Pristiq, Khedezla) Duloxetine (Cymbalta) Levomilnacipran (Fetzima) Venlafaxine (Effexor XR) Milnacipran (Savella, Ixel, Joncia)	Nausea, excessive sweating, dry mouth, loss of appetitedizziness, headache, insomnia,fatigue, sexual dysfunction,increased blood pressure,weight gain, constipation
Tricyclic Antidepressants (TCA)	Norepinephrine, serotonin	reuptake inhibitor (NET and SERT),receptor antagonist (5-HT2)	Doxepin (Sinequan, Quitaxon, Aponal)	Constipation, blurred vision, dry mouth, drowsiness, tremor, drop in blood pressure when moving from sitting to standing, urine retention, weight loss, increased appetite leading to weight gain, sexual dysfunction, excessive sweating, nausea
	Serotonin, norepinephrine	reuptake inhibitor (SERT and NET),receptor antagonist (5-HT2)	Amitryptyline (Elavil)	
	Serotonin, dopamine	receptor antagonist (5-HT2 and D2)	Trimipramine (Surmontil)	
	Norepinephrine	reuptake inhibitor (NET)	Desipramine (Norpramin, Pertofrane) Protriptyline (Vivactil) Nortriptyline (Pamelor, Noritren, Nortrilen)	
	Norepinephrine, serotonin	reuptake inhibitor (NET and SERT)	Amoxapine (Asendin) Lofepramine (Gamanil, Lomont, Tymelyt)	
	Serotonin, norepinephrine	reuptake inhibitor (SERT and NET)	Imipramine (Tofranil, Tofranil-PM) Clomipramine (Anafranil, Clomicalm) Dosulepin (Prothiaden)	
Monoamine Oxidase Inhibitors (MAOI)	Serotonin, norepinephrine, dopamine	enzyme inhibitor (MAO-A and -B)	Isocarboxazid (Marplan, Marplon, Enerzer) Phenelzine (Nardil, Nardelzine)	Dry mouth, nausea, diarrhea, constipation, headache, insomnia, drowsiness, dizziness, involuntary muscle jerks, low blood pressure, sexual dysfunction, weight gain, difficulty starting a urinary flow, muscle cramps, pricking or tingling sensation in the skin
		enzyme inhibitor (MAO-A and -B), releaser (DA, NE)	Tranylcypromine (Parnate)	
		reversible enzyme inhibitor (MAO-A)	Moclobemide (Amira, Aurorix, Clobemix, Depnil, Manerix)	
	Dopamine, norepinephrine, serotonin	enzyme inhibitor (MAO-B and -A)	Selegiline (Emsam)	

(*continued on next page*)

Table 1 (*continued*)

Class (traditional terminology[b]*)*	Pharmacology	Mechanism of action	*Drugs (trade names)*	Side effects
Atypical Antidepressants	Norepinephrine, dopamine	Reuptake inhibitor (NET, DAT), releaser (NE, DA)	Bupropion (Wellbrutin, Zyban)	Headache, agitation, insomnia, loss of appetite, weight loss, sweating
	Norepinephrine, serotonin	Receptor antagonist (NE alpha-2, 5-HT2, 5-HT3)	Mirtazapine (Remeron)	Sedation, increased appetite, weight gain
	Serotonin	Receptor antagonist (5-HT2) receptor agonist (5-HT1A)	Nefazodone (Serzone, Dutonin, Nefadar)	Nausea, diarrhea, constipation, dizziness, drowsiness, insomnia, dry mouth, blurry vision, headache, increased appetite
	Serotonin	Receptor antagonist (5-HT2) receptor agonist (5-HT1A)	Trazodone (Oleptro, Depryl)	Sedation, nausea, priapism (rare)
	Melatonine	Receptor agonist (M1,M2), receptor antagonist (5-HT2B, 5-HT2C)	Agomelatine (Melitor, Thymanax, Valdoxan)	Nausea, insomnia, fatigue, excessive sweating, headache, insomnia, weight gain, liver problems
	Glutamate	Agonist of the μ-opioid receptor	Tianeptine (Stablon, Coaxil)	Headache, dizziness, Insomnia/nightmares, drowsiness, dry mouth

SERT-serotonin transporter, NET- norepinephrine transporter.

[a] Based on information provided by drug manufacturers, (Nbn2r, 2019) and (Ferguson, 2001; Santarsieri and Schwartz, 2015).

[b] New terminology recently proposed (Nbn2r, 2019).

[c] FDA approved to treat obsessive-compulsive disorder, sometimes used to treat depression.

duloxetine, escitalopram, fluvoxamine, fluoxetine, imipramine, sertraline and venlafaxine (Amodeo et al., 2019; Bacaltchuk and Hay, 2003) (Table 2). Of note, lisdexamfetamine, a prodrug of D-amphetamine, is the only FDA-approved medication for binge eating disorder and should, as a rule, be preferred over antidepressants. However, comorbidities such as anxiety or depression may support the use of antidepressants in the first line of treatment.

While use of single antidepressant agents is clinically effective as treatment for bulimia nervosa, it is unsupported as the sole therapeutic intervention for anorexia nervosa (Marvanova and Gramith, 2018). Instead, antidepressants such as fluoxetine, or possibly citalopram, sertraline or mirtazapine, should only be used as adjunctive treatment to nutritional restoration and psychotherapy (Marvanova and Gramith, 2018).

The efficacy of antidepressants as treatment for eating disorders may in part be explained by the role of serotonin, noradrenaline and dopamine systems in the pathophysiology of bulimia nervosa and binge eating disorder (Latagliata et al., 2010; Monteleone et al., 2006; Wang et al., 2011). These systems are the target of most antidepressants.

2.2. Antidepressants as smoking cessation aids

Tobacco use is the leading cause of preventable disease and death in developed countries. Among the 4000 chemical compounds found in tobacco, nicotine is recognized as the chemical that causes addiction, due to induction of changes in the central nervous system (Walker et al., 1990). Nicotine inhaled from cigarettes is absorbed into the bloodstream, crosses the blood-brain barrier and quickly reaches the brain. In the brain, nicotine binds to nicotinic acetylcholine receptors (nAChR) (Bozinoff and Le, 2018). Some nAChR subtypes have been shown to regulate the release of dopamine, noradrenaline and serotonin (Albuquerque et al., 2009). Activation of the dopaminergic brain reward pathway is thought to be critical for the early rewarding and reinforcing effects of nicotine (Koob and Bloom, 1988; Volkow et al., 2009). On the other hand, nicotine withdrawal syndromes have been linked to reduced dopamine levels and deficit of brain reward (Epping-Jordan et al., 1998). Epidemiological studies indicate that nicotine dependence occurs more frequently in people with psychiatric illnesses such as ADHD, depression, schizophrenia, anorexia nervosa and anxiety disorders (Salin-Pascual et al., 2003). Substance abuse is a comorbidity in up to 49% of people with eating disorders (Courbasson and Brunshaw, 2009). Similarly, depression occurs more frequently among chronic smokers than non-smokers, and mood alterations are among the withdrawal symptoms during cessation of tobacco smoking (Breslau et al., 1992; Covey et al., 1997).

Numerous clinical trials have studied the use of antidepressants as smoking cessation aids (Hughes et al., 2004; Shoaib and Buhidma, 2018). Bupropion, an atypical antidepressant, has shown promising results in some trials, demonstrating both good efficacy and higher long-term rates of smoking cessation than use of either placebo or a nicotine patch (Hurt et al., 1997; Jorenby et al., 1999; Martinez-Raga et al., 2003). Although other clinical trials showed no efficacy of bupropion (Killen et al., 2004; Simon et al., 2004), it was still approved as a smoking cessation agent and is used as first-line therapy. Varenicline, an α4β2 nAChR agonist, has similar efficacy as bupropion as a smoking cessation aid. However, bupropion is more cost effective and has a better side-effect profile (Kulaylat et al., 2018).

The mechanism by which bupropion functions is unclear. The leading theory is that bupropion and its metabolites enhance dopaminergic and noradrenergic transmission by blocking reuptake of neurotransmitters at the synapse (Damaj et al., 2004; Paterson et al., 2007). The antidepressant can also act as an nAChR antagonist by inhibiting the stimulant effect of nicotine (Slemmer et al., 2000).

Drugs from all five classes of antidepressants have been investigated for use as smoking cessation aids (Shoaib and Buhidma, 2018). The second generation TCA nortriptyline is regarded as the most promising

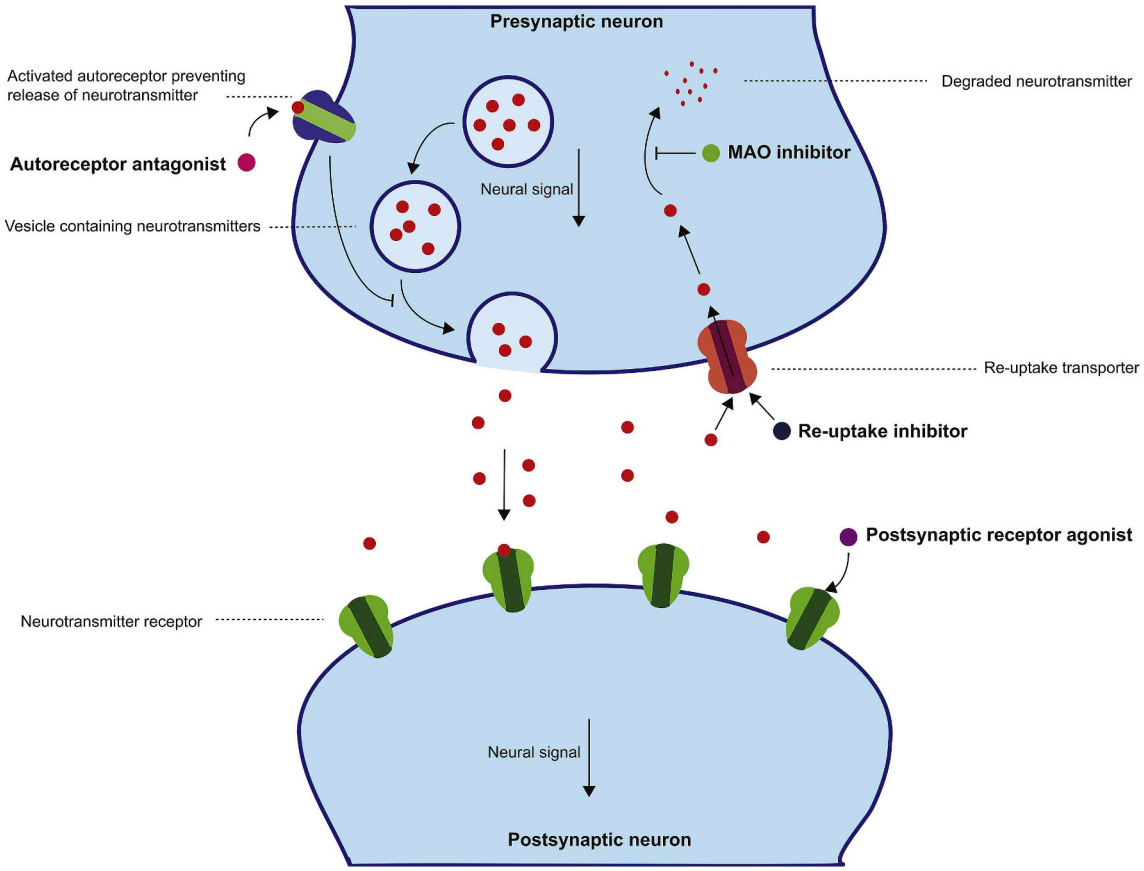

Fig. 2. Modulation of neurotransmitter levels by drugs for depression.
Neurotransmitters are released by the presynaptic neurons, bind to, and react with the receptors on the surfaces of other neurons. The neurotransmitters also bind to autoreceptors on the presynaptic cell and, via a negative feedback loop, trigger a reduction in the release of a certain neurotransmitter. Part of the neurotransmitters are taken back up into the presynaptic cell via re-uptake transporters and degraded by the monoamine oxidase (MAO). Antidepressants enhance the levels of neurotransmitters by targeting one of these reactions. The neurotransmitter can then activate the postsynaptic cell.

alternative to bupropion. This antidepressant mainly inhibits noradrenaline and serotonin transporters (Kripke, 2005). Antidepressants of the SSRI category are not effective, however, suggesting that serotonin does not play the main role in smoking addiction (Hughes et al., 2014). Further research is needed to establish which antidepressants or classes of antidepressants are effective in smoking cessation. This will shed light on the biological factors controlling nicotine dependence and smoking.

2.3. Antidepressants in chronic pain management

Chronic pain is a major public health problem, seriously affecting the patient's daily routines and decreasing the quality of life (Duenas et al., 2016). It is estimated that between 11 and 50% of the American and British populations may suffer from chronic pain of various origins (Dahlhamer et al., 2018; Fayaz et al., 2016). In parallel to standard medications such as paracetamol, codeine or tramadol, antidepressants are commonly prescribed for the treatment of several chronic pain conditions, also when depression is not a factor. However, for such medical interventions, the dose of antidepressants are generally lower than what is required to reveal anti-depressive effects (Riediger et al., 2017). This applies in particular to TCAs, which effectiveness at low doses is higher than of other groups of antidepressants.

One of the most common antidepressants used for treatment of chronic pain is duloxetine. The effectiveness of this SNRI has been proven in multiple double-blind, placebo-controlled trials (Skljarevski et al., 2011). The use of duloxetine in patients with painful chemotherapy-induced peripheral neuropathy results in a significantly greater reduction in pain compared to placebo treatment (Smith et al., 2013). A similar outcome is observed in patients suffering from pain associated with diabetic peripheral neuropathy (Ormseth et al., 2011; Raskin et al., 2006; Schoenberger et al., 2006), chronic lower back pain (Schukro et al., 2016), or osteoarthritis (Skljarevski et al., 2011).

Solid evidence from numerous randomised controlled trials demonstrate that TCAs are among the most effective drugs for treatment of different neuropathic pain conditions (Sindrup et al., 2005). TCAs were for the first time introduced as treatment for painful diabetic neuropathy more than 40 years ago (Davis et al., 1977) and since then, their analgesic effects have been proven repeatedly in a number of neuropathic pain conditions (Kishore-Kumar et al., 1990; Max et al., 1987, 1988, 1992). TCAs' neuropathic pain relieving effects, both in patients with and without depression, are most likely achieved by inhibition of presynaptic reuptake of serotonin and noradrenaline but also through mechanisms involving N-methyl-D-aspartate receptors and ion channels blockade (Sindrup et al., 2005).

Antidepressants, particularly TCAs and SNRIs, have also found their application in relieving pain related with fibromyalgia (Moret and Briley, 2006). Fibromyalgia is a common, but still poorly understood, disorder characterized by musculoskeletal pain accompanied by other symptoms such as fatigue, sleep, and memory and mood problems (Clauw, 2015; O'Malley et al., 2000). Since it is often comorbid with psychiatric disorders, such as anxiety and depression, and other therapeutic options are limited antidepressants are frequently used as the first-line treatment (Moret and Briley, 2006; O'Malley et al., 2000). It is worth to highlight that the effectiveness of antidepressants used for treating fibromyalgia appears to be independent of their effect on

Table 2
Off-label uses of drugs for depression.

Off-label use	Drugs	Mechanism of action	Reference
Hives (urticaria)	Doxepin	Antihistamine/blocks histamine receptor	Goldsobel et al. (1986)
Chronic pain of fibromyalgia	Amitriptyline	Unknown	Moore et al. (2012)
	Duloxetine[a]	Increase levels of noradrenaline, serotonin and norepinephrine	Hauser et al. (2014)
	Milnacipran[a]		
Chronic pain associated with diabetic peripheral neuropathy	Dulexetine[a]	Unknown	(Ormseth et al., 2011; Skljarevski et al., 2011)
Pain associated with rheumatoid arthritis	Amitriptyline	Unknown	(Perrot et al., 2008; Richards et al., 2011)
	Paroxetine	Unknown	(Krishnadas et al., 2011; Richards et al., 2011)
	Escitalopram		
Urinary incontinence	Amitriptyline	Relieve pelvic floor spasms/muscle dysfunction, increase level of serotonin	(Andersson et al., 1999; Pranikoff and Constantino, 1998)
	Imipramine		
	Duloxetine	Contracting the urethral sphincters	Sweeney and Chancellor (2005)
Eating disorders	Fluoxetine	Regulates the body's hunger signals	(Flament et al., 2012; Hudson et al., 1996; McElroy et al., 2012)
	Sertraline		
	Imipramine	Unknown	(Aigner et al., 2011; Flament et al., 2012; Hudson et al., 1996)
	Trazadone	Unknown	Hudson et al. (1996)
	Citalopram	Unknown	McElroy et al. (2012)
	Duloxetine		
	Escitalopram		
Premature ejaculation	Sertraline	Side effects include erectile dysfunction and inability to ejaculate	(Arafa and Shamloul, 2006; Balon, 1996; McMahon, 1998)
	Paroxetine		
	Fluoxetine		
	Escitalopram		
	Clomipramine	Unknown	Haensel et al. (1996)
Premenstrual dysphoric disorder	Fluoxetine	Changes how the body converts progesterone to allopregnanolone	Shah et al. (2008)
	Sertraline		
	Citalopram		
	Paroxetine		
Hot flashes during menopause	Escitalopram	Unknown	(Barton et al., 2010; LaCroix et al., 2012)
	Citalopram		Stearns et al. (2003)
	Paroxetine		
	Venlafaxine	Unknown	(Archer et al., 2009; Joffe et al., 2014; Loprinzi et al., 2000; Pinkerton et al., 2013; Speroff et al., 2008)
	Desvenlafaxine[b]		
Migraine prevention	Amitriptyline	Unknown	(Holroyd et al., 2001; Jackson et al., 2010)
	Nortriptyline		
	Venlafaxine	Unknown	(Liu et al., 2017; Ozyalcin et al., 2005; Young et al., 2013)
	Duloxetine		
Smoking cessation	Bupropion[a]	Unknown	(Hughes et al., 2014; Kripke, 2005)
	Nortriptyline	Unknown	(Hughes et al., 2014; Kripke, 2005)
Sleeping disorders	Amitriptyline	Sedative	(Everitt et al., 2014; Pagel and Parnes, 2001; Rojas-Fernandez and Chen, 2014; Weber et al., 2010)
	Doxepin		
	Mirtazapine	Block histamine receptor	(Jaffer et al., 2017; Pagel and Parnes, 2001)
	Trazodone		
ADHD	Desipramine	Blocks the reuptake of norepinephrine and serotonin in the presynaptic neuronal membrane	(Osland et al., 2018; Otasowie et al., 2014)

[a] FDA approved for this indication.
[b] Desvenlafaxine was withdrawn from Europe in 2009 for medical use.

comorbid depression (Hauser et al., 2009; Moret and Briley, 2006). The most common fibromyalgia treatment strategies are TCAs (e.g. amitriptyline); however, their major disadvantage is their low tolerability (Hauser et al., 2014; Moore et al., 2012; Moret and Briley, 2006). SNRIs, in turn, are much better tolerated and their effectiveness is comparable to TCAs (Moret and Briley, 2006). By now only two SNRIs, duloxetine (cymbalta) and milnacipran (savella), are officially approved by the FDA for the treatment of fibromyalgia (Hauser et al., 2014). Savella, even though it acts like other SNRIs, is not used to treat depression. A third FDA approved drug for fibromyalgia is the anticonvulsant medicine pregabalin (lyrica) (Boomershine, 2010). Interestingly, SSRIs and MAOIs do not seem to be effective in treating fibromyalgia, which suggests that there probably exists a dysregulation of both serotonin and norepinephrine neurotransmission in this disorder (Hauser et al., 2009; Moret and Briley, 2006).

Antidepressants are also regularly applied in clinical practice to treat chronic pelvic pain syndrome (Lee et al., 2005; Papandreou et al., 2009). Particularly, the SSRI sertraline is well documented to lead to a significant improvement in prostatic symptom severity and frequency (Lee et al., 2005). Other antidepressant drugs for the management of urological chronic pelvic pain include amitriptyline, nortriptyline, duloxetine and citalopram (Papandreou et al., 2009). Interestingly, milnacipran was reported to reduce phantom limb pain after amputation of injured or diseased limbs (Chalana, 2010; Nagoshi et al., 2012).

Chronic pain is often an inseparable part of rheumatoid arthritis (RA) and unfortunately, there is currently no cure for RA. Therefore, treatments of RA are aimed only to relieve the pain and improve the patients' ability to move. As in the case of previously discussed chronic pain conditions, RA is also managed with antidepressants. In particular, amitriptyline can be recommended by rheumatologists for pain caused by RA (Bernstein, 2019). Although there exist several studies comparing antidepressant therapy with other RA treatments (including placebo and non-pharmacological therapies), unfortunately no reliable conclusions about the antidepressants' efficacy can be drawn from these trials (Richards et al., 2011). There is only one case study, describing a patient who was treated for major depression and whose RA symptoms remitted after use of escitalopram (SSRI) (Krishnadas et al., 2011). Therefore, more high quality clinical trials are required in this field to fully support prescription of antidepressants for patients with RA.

The mechanisms explaining how antidepressants reduce the pain

are still not fully understood. The most straightforward explanation is that these drugs increase the levels of neurotransmitters in the spinal cord which then reduce pain signals. However, antidepressants are known to be slow-acting. Pain relief from these drugs may be felt only after weeks of treatment, and the reduction of pain is rather moderate (Mayo Clinic, 2016). In support of this hypothesis, it has been shown that mainly noradrenaline is responsible for inhibiting neuropathic pain (Obata, 2017). An increased level of noradrenaline in the spinal cord reduces pain through the α2-adrenergic receptors and targets the locus coeruleus, improving the function of an impaired descending noradrenergic inhibitory system. Dopamine and serotonin may aid to enhance the effect of noradrenaline in reducing neuropathic pain (Obata, 2017).

Several other possible mechanisms exist by which antidepressants may reduce pain. Antidepressants can block sodium channels (Dick et al., 2007), which in turn inhibit discharges occurring in damaged nerves thereby leading to neuropathic pain reduction (Zuliani et al., 2010). Some antidepressants may also act as antagonists of N-methyl-D-aspartate (NMDA) receptors (Barygin et al., 2017) responsible for central sensitization in certain types of neuropathic pain (Herrero et al., 2000). Additionally, TCAs are reported to block calcium channels, activate potassium channels, inhibit production of nitric oxide and prostaglandin, and alter GABA-B receptor functions (Obata, 2017). All these actions of antidepressants may to some extent be responsible for reducing neuropathic pain.

2.4. Antidepressants for migraine prevention

Migraine is among the top three most prevalent medical conditions in the world and is the seventh leading cause of time spent disabled worldwide, significantly diminishing the quality of life (Global Burden of Disease Study, 2015). Migraine is also associated with an increased risk of other disorders, including asthma, stroke, anxiety and depression (Charles, 2017; Minen et al., 2016; Vetvik and MacGregor, 2017). It should not be confused with a regular, strong headache. Migraine is an episodic, recurrent headache characterized by recurrent attacks of severe and mostly undulating pain. It is typically accompanied by nausea, photophobia, phonophobia and vision problems (Mayo Clinic, 2019). Therapies for acute migraine include triptans, nonsteroidal anti-inflammatory drugs, and antiemetic agents (Charles, 2017). Different strategies are used as prophylaxis to prevent migraine attacks. They include candesartan, beta-blockers, anticonvulsant agents, botulinum toxin, as well as antidepressants (Charles, 2017). Preventive treatments of migraine may also include nutritional supplements, lifestyle alterations, surgery or stress management therapy (Gilmore and Michael, 2011; Holroyd et al., 2001).

Although antidepressants are not the first-line prophylactic strategy for patients with migraine, several clinical trials have proven their effectiveness in the treatment of migraine and related headache disorders (Koch and Jurgens, 2009). Especially TCAs: amitriptyline (Couch and Hassanein, 1979; Jackson et al., 2010; Kalita et al., 2013) and nortriptyline (Holroyd et al., 2001; Jackson et al., 2010) have the best evidence for use in migraine prevention. When amitriptyline is not tolerated by patients, treatment is continued with nortriptyline (Burch, 2019). SNRIs also show efficacy and may even be the most effective treatment in patients with comorbid depression and migraine (Burch, 2019). Especially venlafaxine is often used with success as a prophylactic drug in ameliorating symptoms in migraine patients (Liu et al., 2017; Ozyalcin et al., 2005; Salviz et al., 2016). Duloxetine, another SNRI, demonstrates effectiveness as a headache preventive medication only at high doses (Taylor et al., 2007; Young et al., 2013). SSRIs including fluoxetine (Prozac) do not seem to be potent in migraine prevention (Burch, 2019).

2.5. Use of antidepressants to alleviate sleep disorders

The major part of all off-label prescribed drugs are antidepressants used to treat insomnia. Insomnia is the most commonly encountered sleep disorder that, according to multiple world-wide studies, is experienced by 10–50% of the population (Bhaskar et al., 2016). Transient insomnia is estimated to affect even up to 80% of the population, whereas chronic insomnia is diagnosed in 15% of the population (Pagel and Parnes, 2001). Interestingly, a high fraction of patients with chronic insomnia also has depressive symptoms and *vice-versa*; chronic insomnia itself can lead to depression (Breslau et al., 1996; Pagel and Parnes, 2001). There exist several FDA approved medications to treat insomnia including benzodiazepines (dizapepam), non-benzodiazepines (ambien) and selective-melatonin receptor agonist (ramelteon). Despite the availability of these drugs, among the most popular treatments for insomnia are antidepressants. Interestingly, only one antidepressant, doxepin, has obtained FDA approval for this indication (Lai et al., 2011).

Among TCAs, doxepin (sinequan) appears to be best suited for managing insomnia in healthy adults. Doxepin works as a selective antagonist to H(1) receptors, which promote the initiation and maintenance of sleep (Owen, 2009) (Table 2). Ultra-low doses of this drug (< 6 mg per day) significantly improve and sustain both maintenance and duration of sleep (Rojas-Fernandez and Chen, 2014; Weber et al., 2010). Another frequently prescribed TCA is amitriptyline, which as a long-term option is found to be effective for patients with ongoing sleep problems (Everitt et al., 2014; Pagel and Parnes, 2001).

An adequate amount of data also supports the efficacy and general safety of the use of two atypical antidepressants, mirtazapine (remeron) and trazodone (oleptro) (Jaffer et al., 2017; Pagel and Parnes, 2001). Low doses of trazodone have been demonstrated to be suitable for the treatment of primary insomnia, as well as secondary insomnia, resulting from depression or other medical issues (Jaffer et al., 2017). Mirtazapine, in contrast, is administered at higher doses, similar to those for treatment of depression, thus it is often considered as single-agent therapy for people with insomnia and co-morbid depression (Minkel and Krystal, 2013).

TCA antidepressants (e.g. amitriptyline, imipramine, or nortriptyline) act as sedatives. They block the reuptake of serotonin and norepinephrine, which are associated with the sleep-wake cycle. Additionally, they may block histamine receptors (including H1, 5-HT2A and the α-2 adrenergic receptors) which cause sleepiness. Interestingly, SSRIs generally show an opposite trend as they are known to induce insomnia (Pagel and Parnes, 2001). However, it should be kept in mind that sedative effects can be observed also in a small group of patients treated with SSIRs, in particular with paroxetine (Marken and Munro, 2000).

Insomnia, although very common, is not the only sleep disorder treated by antidepressants. Sleep paralysis, which is a temporary inability to move or speak after waking up or falling asleep, can be completely stopped by clomipramine (Shapiro, 1975). This antidepressant works by altering rapid eye movement (REM) sleep and may be suggested by doctors, particularly in cases of severe sleep paralysis (National Health Service, 2016). Antidepressants are also found to be efficacious in treating narcolepsy. Early trials provided evidence for using antidepressants only to counteract cataplexy, one of the symptoms of narcolepsy (Vignatelli et al., 2008). Most recently, fluoxetine, sertraline and venlafaxine were shown to be effective in treating both symptoms of narcolepsy: excessive daytime sleepiness (EDS) and cataplexy (Jin et al., 2019).

Since TCA antidepressants are known to suppress REM sleep, escitalopram, sertraline, duloxetine and paroxetine are proposed for the treatment of nightmares associated with posttraumatic stress disorder (Aurora et al., 2010). Antidepressants are also used in the treatment of disorders related to the deepest stage of non-rapid eye movement (NREM) sleep, such as night terrors (also known as sleep terrors) and

sleepwalking (occurring frequently together with night terrors) (Touchon, 1995). Night terrors are classified as a parasomnias, which affect almost 40% of children and only a small percentage of adults. Although treatment of night terrors, particularly for children, isn't usually necessary, use of medication such as benzodiazepines or certain antidepressants is found to be effective (Mayo Clinic, 2018; Touchon, 1995).

There is however always another side of the coin. Patients taking antidepressants are also reported to develop various parasomnias (Kierlin and Littner, 2011). The most frequent sleep disorder experienced after using antidepressants is REM sleep behavior disorder (RBD). Others include nightmares, sleepwalking, night terrors, sleep related eating disorders and hypnagogic/hypnopompic hallucinations (Kierlin and Littner, 2011). Taking into consideration all these dangers, as well as other side effects of antidepressants, together with the risk of overdose, one should always consider the possibility of different treatments. Psychological therapies, such as cognitive behavioral therapy, are one of the options for the management of insomnia and other sleep disorders (Everitt et al., 2014).

2.6. Other off-label uses of drugs for depression

The list of health issues for which antidepressants are being applied off-label is not limited to examples described above (Table 2). Drugs for depression are also commonly used for stress urinary incontinence, a major urologic problem that affects mostly women. For its treatment, duloxetine (Sweeney and Chancellor, 2005; Weinstein et al., 2006), imipramine (Andersson et al., 1999; Gilja et al., 1984) and amitriptyline (Pranikoff and Constantino, 1998) are being prescribed. Doxepin, an H1 and H2 histamine receptor antagonist, has been administrated for over 30 years to treat and prevent chronic idiopathic urticaria (hives) (Goldsobel et al., 1986; Greenberger, 2014; Greene et al., 1985).

SSRIs including paroxetine, fluoxetine and escitalopram have been found as effective treatment for patients with premature ejaculation (Arafa and Shamloul, 2007). Premature ejaculation is also treated with clomipramine and sertraline (Balon, 1996; McMahon, 1998), as well as with dapoxetine, a member of the SSRI family, which is however not used to treat depression (Andersson et al., 2006). Solid evidence justifies also uses of antidepressants for lessening hot flashes during menopause. This includes citalopram (Barton et al., 2010), escitalopram (LaCroix et al., 2012), paroxetine (Stearns et al., 2003) and desvenlafaxine (Archer et al., 2009; Pinkerton et al., 2013; Speroff et al., 2008). SSRIs, in turn, were found to be effective in relieving symptoms of premenstrual dysphoric disorder (Eriksson et al., 1995; Shah et al., 2008). Antidepressants (TCAs) are also reported to be therapeutically useful as second line of treatment in the reduction of symptoms of attention deficit hyperactivity disorder (ADHD) (Otasowie et al., 2014; Wilens et al., 1995).

3. A new class of antidepressants

The FDA recently approved the S-enantiomer of ketamine, esketamine, for treatment-resistant depression (Kim et al., 2019). This is an interesting development in the field of antidepressants as it introduces a whole new class of antidepressants. Ketamine is also known as the party drug Special K and can be used as a hallucinogen. It is a noncompetitive antagonist of the glutamate receptors of the N-methyl-D-aspartate (NMDA) type, and was approved as an anesthetic in 1970. Following studies showed that ketamine can act as an antidepressant with rapid effect (within hours) (Kavalali and Monteggia, 2012). As most antidepressants need several weeks to induce a clinical response, this is an attractive property.

The exact mechanism of action of ketamine is unclear. Although the antidepressant effects may be mediated by several mechanisms beyond NMDA receptor antagonism (Molero et al., 2018), the pharmaceutical industry has focused on this property when developing pharmaceutical versions of ketamine. Esketamine shows an approximately fourfold enhanced binding affinity for the NMDA receptor compared to ketamine, and has a similar antidepressant effect (Molero et al., 2018). While the FDA has not approved ketamine for treatment of depression, an estimated 300 clinics in the United States are providing ketamine off-label to depression patients (Reardon, 2018).

A major safety concern for both ketamine and esketamine is the potential for abuse. The FDA has addressed this by approving esketamine with a Risk Evaluation and Mitigation Strategy (REMS). This means that esketamine can only be provided by clinics and hospitals that are certified in the REMS (Kim et al., 2019). The approval of esketamine for depression will likely result in other uses of the drug. So far, only a moderate number of studies have been performed on esketamine. In contrast, more than 800 clinical trials involving ketamine are registered at clinicaltrials.gov, including studies on migraine, pain, autism, obsessive-compulsive disorder, social anxiety and obstructive sleep apnea syndrome. It will be of high interest to follow the development of off-label uses of this class of antidepressants.

4. Summary

The use of antidepressants has shown a rapid increase in western countries over the last years. This is in part due to their many off-label uses (Table 2). While these therapies provide treatment options for patients where there were previously few or none, it is important to keep in mind that they have several side effects which may reduce the quality of life for the affected patient (Table 1). For many of the off-label conditions, depression is a comorbidity. The antidepressants may therefore in these cases treat symptoms of the disease, while additional therapy is needed to treat the underlying cause. In the case of eating disorders, this includes nutritional restoration and psychotherapy (Marvanova and Gramith, 2018), whereas for sleep disorders the cognitive behavioral therapy and better sleep hygiene may be recommended (Everitt et al., 2014).

Antidepressants are not considered addictive (Haddad, 1999). A larger problem is discontinuation of therapy due to lack of acute effects. This picture is changing with the approval of esketamine, a fast-acting antidepressant developed from the hallucinogen ketamine. While the FDA has taken precautions, there is potential for abuse.

It will be of interest to follow the future development and use of antidepressants. The approval of novel drugs and the high number of clinical studies involving this class of therapies suggest that they will play a central role in medicine for years to come.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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