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Use of amitriptyline, bupropion and agomelatine in the treatment of non-depressive disorders: a review of mechanisms and therapeutic indications

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Abstract

Introduction

Antidepressants such as amitriptyline, bupropion and agomelatine are widely used not only in the treatment of depression, but also in other conditions. Their mechanisms of action affect different neurotransmitter systems, allowing their use in the treatment of pain, addiction or sleep disorders. Amitriptyline, which is a tricyclic antidepressant, has strong analgesic effects. Bupropion, a dopamine and norepinephrine reuptake inhibitor, helps in the treatment of addiction and ADHD. Agomelatine, a melatonin receptor agonist, has been shown to regulate diurnal rhythms, making it useful in the treatment of insomnia and other sleep disorders.

Aim of the Study

The aim of this study is to analyse the use of amitriptyline, bupropion and agomelatine in the treatment of conditions other than depression, with a focus on their mechanisms of action and clinical efficacy.

Materials and Methods

An analysis of PubMed papers was conducted using keywords: antidepressants, tricyclic antidepressants, SSRI, amitriptyline, bupropion, agomelatine.

Basic Results

Amitriptyline is highly effective in the treatment of neuropathic pain, migraines and insomnia due to its potent action on serotonin and histamine receptors. Bupropion is used in the treatment of nicotine addiction and ADHD, as it acts on the dopaminergic and noradrenergic systems to improve concentration and impulse control. Agomelatine, as a melatonin receptor agonist, is used to regulate diurnal rhythms, making it helpful in the treatment of sleep disorders and adaptation to time zone changes. Each of these drugs has unique properties that go beyond their primary use in depression.

Conclusion

Amitriptyline, bupropion and agomelatine are antidepressants that are used for a variety of conditions beyond depression. Amitriptyline is effective in treating neuropathic pain and insomnia, bupropion aids in the treatment of nicotine addiction and ADHD, and agomelatine helps regulate diurnal rhythms. Each of these drugs acts on different neurotransmission mechanisms, which determines their diverse clinical applications. Their versatility allows individualisation of therapy according to the patient's needs. Further research may contribute to a better understanding of their potential applications and optimisation of therapy.

Key words: antidepressants, tricyclic antidepressants, SSRI, amitriptyline, bupropion, agomelatine.

Introduction

Antidepressants, although originally used for depression, are finding use in the treatment of many other psychiatric and somatic conditions. Modern pharmacology is increasingly exploring their potential actions in the context of disorders that are not directly related to mood. The antidepressants used in such cases, such as tricyclic antidepressants (TCAs), bupropion or agomelatine, are characterised by a variety of mechanisms of action that allow them to be effective in the treatment of different pathological conditions [1].

Tricyclic antidepressants, which include amitriptyline, mainly act by blocking the reuptake of serotonin and norepinephrine, leading to an increase in the concentration of these neurotransmitters at brain synapses. As a result, they not only have an antidepressant effect, but also an analgesic effect, which makes them often used in the treatment of neuropathic pain, migraines or fibromyalgia. Amitriptyline is one of the best-known representatives of this

group of drugs and is widely used in the treatment of chronic pain, sleep disorders and anxiety [1, 2].

In contrast, bupropion, which is a dopamine and norepinephrine reuptake inhibitor, differs in its mechanism of action from classic antidepressants. Due to its unique properties, bupropion is used not only in the treatment of depression, but also as an adjunct in the treatment of nicotine dependence and in the treatment of attention deficit hyperactivity disorder (ADHD) [1, 3, 4].

Agomelatine, on the other hand, acts as an agonist of melatonin receptors (MT1 and MT2) and an antagonist of serotonin 5-HT2C receptors, thereby regulating the diurnal rhythm and improving sleep quality. This makes agomelatine particularly effective in patients with depression accompanied by sleep disorders, but it is also used in the treatment of anxiety disorders and post-traumatic stress disorder (PTSD) [1, 5].

All the drugs mentioned have much broader applications than just treating depression, due to their diverse mechanisms of action and effects on the nervous system. Examples of their use in other conditions, such as pain disorders, anxiety disorders or sleep disorders, show that antidepressant pharmacotherapy can be an effective tool in the treatment of various health problems.

AMITRIPTYLINE

General information

Tricyclic antidepressants such as amitriptyline work by inhibiting the reuptake of norepinephrine and serotonin, but unlike selective serotonin reuptake inhibitors (SSRIs), they have a broader action, affecting different neurotransmitters. Amitriptyline is a tertiary amine, blocking not only serotonin and norepinephrine reuptake, but also acting on other receptors such as muscarinic (cholinergic), histamine H1 and α1-adrenergic receptors. This makes the drug exhibit a number of additional effects, such as sedative, analgesic and sleep-inducing effects [6, 7].

Pharmacokinetics

Amitriptyline is well absorbed after oral administration, with a bioavailability of 30-60%. It also has a high volume of distribution after intravenous administration, and the drug can cross the placental barrier. Amitriptyline is metabolised to nortriptyline predominantly by

the enzyme CYP2C19, with CYP3A4 and CYP2B also involved in its metabolism: CYP3A4 and CYP2D6. The half-life ranges from 10 to 28 hours, and the excretion of the drug and its metabolites is mainly via the kidneys [7].

Indications for use

Amitriptyline is used for the treatment of depression, but also for the treatment of anxiety disorders, migraine pain, chronic neuropathic pain and the prevention of tension and migraine headaches in adults. It is also sometimes used to treat bedwetting in children and the elderly [6, 9].

Side effects

Amitriptyline, despite its efficacy, also has potential side effects associated with receptor blocking. The most common side effects include weight gain and gastrointestinal symptoms such as constipation and dry mouth. By blocking alpha-adrenergic receptors, it can cause orthostatic hypotension, dizziness and sedation. It can also lead to cardiac arrhythmias, slowed cardiac conduction and QTc prolongation. By acting on histamine H1 receptors, it increases somnolence, appetite and body weight. It lowers the seizure threshold, so caution should be exercised in patients with epilepsy, especially at higher doses [7, 8].

Use in children

Amitriptyline is not recommended for the treatment of depression in patients under 18 years of age, as there are no data to support its safety and efficacy in this age group. However, it can be used to treat bedwetting in children over 6 years of age, provided organic causes (e.g. spina bifida) have been ruled out and when other treatments, such as decongestants or vasopressin analogues, have proved ineffective [9].

Use in irritable bowel syndrome

A study was conducted in 55 primary care settings in England between 2019 and 2022, involving 463 adult patients with IBS. Participants received low-dose amitriptyline (10-30 mg) or placebo for 6 months. The results showed that amitriptyline was more effective than placebo in relieving IBS symptoms (as assessed by the IBS-SSS), this mainly concerned pain relief. Amitriptyline was safe and relatively well tolerated, with some patients experiencing

mild side effects. The results of the study suggest that low-dose amitriptyline should be offered to patients in whom first-line treatment is ineffective [10].

Tension-type headache

Tension-type headache, is the most common type of primary headache, affects approximately 80% of the population, and has significant socio-economic implications due to its prevalence. It is characterised by bilateral, compressive or tension-type pain of mild to moderate intensity, without additional symptoms. Two main treatment strategies are used: acute treatment and prophylactic treatment. Tricyclic antidepressants, including amitriptyline, are most commonly used for prophylaxis and their efficacy has been confirmed in many clinical trials. Amitriptyline (in doses of 10-100 mg daily) has been shown to be effective in the prevention of pain, as low doses are used, the treatment is well tolerated by patients, with minimal side effects. Combining amitriptyline with other medications and behavioural therapies may be particularly effective [11, 12].

Neuropathic pain

Neuropathic pain is a type of pain that results from damage or disturbance in the somatosensory part of the nervous system. This damage can involve both the central and peripheral parts of the nervous system. It is characterised by a pathological course and often does not respond to traditional analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen), metamizol or paracetamol. Typically, neuropathic pain is chronic in nature. The first-choice drugs for its treatment are tricyclic antidepressants (e.g. amitriptyline), serotonin and norepinephrine reuptake inhibitors (e.g. duloxetine), as well as pregabalin and gabapentin.

The effects of amitriptyline on norepinephrine, sodium channels and NMDA receptors are well-known mechanisms responsible for the reduction of neuropathic pain, as well as the prevention of chronic tension headaches and migraine. Its analgesic effect is not associated with antidepressant properties. A study was conducted between March 2022 and June 2023, which included patients over 18 years of age with complaints of neuropathic lower back pain, spinal cord injury and fibromyalgia. A total of 270 patients participated in the study and were randomly assigned to different treatment groups. Group A received gabapentin 300 mg, group B received pregabalin 75 mg and group C received amitriptyline 10 mg. Pain levels were

assessed at three different times: at baseline (day 0), after 15 days and after 30 days. The results showed that all three therapies had similar efficacy in reducing pain and that the differences between them were not statistically significant, which is in line with previous studies. The study confirmed that amitriptyline, gabapentin and pregabalin had similar efficacy in pain relief. Gabapentin caused fewer side effects, which promotes better co-operation of patients during long-term therapy. The authors point out that the study was conducted on a relatively small group of patients, which may reduce the value of the results obtained; a study on a larger number of patients should be conducted [6, 9, 13, 14].

A meta-analysis of data on the topical use of amitriptyline for neuropathic pain was conducted. The conclusions of the analysis were inconclusive; controlled clinical trials do not support the efficacy of topical amitriptyline in the treatment of neuropathic pain. The results of uncontrolled studies suggest some efficacy, and cases of patients with a tritherapeutic effect have been described, but these may not be reliable due to the lack of control groups and concomitant use of other analgesics by the study subjects [15].

We compared the efficacy of amitriptyline and pregabalin in the treatment of pain in diabetic neuropathy, these being the two main drugs used for this condition. Painful diabetic neuropathy affects approximately 6-34% of all patients with diabetes. A meta-analysis of six studies that met the inclusion and exclusion criteria showed that there were no significant differences between amitriptyline and pregabalin in their effects on pain relief and quality of life. The drugs showed similar side effects and symptoms after drug withdrawal [19]. In addition to amitriptyline and pregabalin, other drugs such as duloxetine, gabapentin and opioids are used in the treatment of diabetic neuropathic pain. Capsaicin is also used in topical treatment. Studies show that the best therapeutic effect comes from using a combination of two or three drugs. This relieves pain more effectively, allows lower doses to be used and thus reduces the risk and severity of side effects [20].

Bed-wetting

Bedwetting is a disorder that causes social difficulties and stress, affecting approximately 15-20% of children aged five years and up to 2% of young adults. The results of an analysis of 54 studies involving 3379 children show that amitriptyline is effective in treating bedwetting in children, acting through its anticholinergic properties that affect bladder tone; unfortunately, after treatment, the problem returned in many children. The recommended doses of amitriptyline for children aged 6 to 10 years range from 10 mg to 20 mg per day,

with the most appropriate form of the drug being chosen for this age group. Children aged 11 years and older should take a dose of 25 mg to 50 mg daily. Before initiating treatment in children in this age group, an ECG examination is necessary to exclude long QT syndrome. The maximum duration of a treatment cycle should not exceed 3 months. If further cycles are needed, medical follow-up should be carried out every three months. Discontinuation of treatment should be gradual, by gradually reducing the dose of amitriptyline. [9, 17]

The case of a 35-year-old patient, diagnosed with paranoid schizophrenia for 10 years, who started clozapine therapy is described. Over four weeks, the dose of clozapine was gradually increased to 400 mg daily. At this dose, the patient reported the onset of daily bedwetting. During the same period, he also noted troublesome salivation, which occurred both at night and during the day. Amitriptyline 25 mg before bedtime was used to control both symptoms. After only four days, the bedwetting had completely disappeared and the nocturnal salivation was significantly reduced [16].

Anticholinergic drugs should be used with caution, especially in patients with a history of strabismus. A case is described of a 9-year-old boy operated on for divergent strabismus who developed bedwetting after surgery and was treated with amitriptyline. The boy most likely developed double vision and convergent strabismus as a result of the drug. After discontinuation of the drug, the symptoms were relieved, but the anticholinergic effect could not be completely reversed [18].

BUPROPION

General information

Bupropion, is an ammonium ketone antidepressant that is used in the treatment of depression and seasonal affective disorder, and as an adjunctive therapy during smoking cessation. It was patented in 1974 and was approved in 1985. Until 2000, it appeared under the name amfebutamone [21, 22].

Bupropion is one of the other antidepressants. Its mechanism is not fully understood. It is a relatively weak reuptake inhibitor of dopamine, norepinephrine and serotonin, while it has no activity against monoamine oxidase. It shows a very weak sedative effect. Its use is rarely followed by anticholinergic symptoms, as well as cardiovascular symptoms or sexual dysfunction [6, 22].

Pharmacokinetics

Bupropion is relatively rapidly absorbed from the gastrointestinal tract. Its maximum serum concentration depends on the form of the drug, i.e. 2 hours for immediate-release, 3 hours for sustained-release, and 5 hours for extended-release. The duration of action is between 1-2 days, with the onset of therapeutic effect occurring after approximately 2 weeks of drug intake. The mean volume of distribution is 19 l/kg, this relatively high value can be attributed to the lipophilic structure of the drug.

Bupropion is metabolised in the liver by CYP2B6 to hydroxybupropion, while non-CYP enzyme-related metabolism leads to erythro-hydrobupropion and treo-hydrobupropion. The activity of the metabolites is 20-50% relative to the original compound. Most of the drug is excreted via the kidneys. Bupropion and its three main metabolites have also been found to cross the blood-brain barrier and subsequently bind to dopamine transporters. The presence of bupropion has also been demonstrated in placental tissue and umbilical cord blood [21, 23].

Indications and contraindications

The indications for the use of bupropion, are depression in adults, seasonal affective disorder and for smoking cessation. The drug is contraindicated in patients with epileptic seizures or in situations predisposing to them, e.g. cessation of alcohol abuse or after withdrawal from sedatives. Bupropion should not be used by patients with a positive history of bulimia and anorexia nervosa [21].

Adverse effects

At recommended doses, bupropion is well tolerated by patients. The most common adverse effects are insomnia, headache, nausea, rhinitis and dry mouth. Patients with a lowered seizure threshold for various reasons should be treated with particular caution, as bupropion may induce an epileptic seizure. The risk of seizures at doses ≤450 mg/day is 0.35-0.44%. Other effects include tachycardia, muscle pain, hallucinations and agitation. A few cases of serotonergic syndrome have also been reported when the drug is used in combination with drugs that increase serotonin blood levels [6,23].

Nicotine addiction

Bupropion is a drug that can be used in patients to treat smoking cessation. Nicotine activates cholinergic receptors, which triggers the release of dopamine, among other things.

Everything happens in areas of the brain associated with reward, more specifically the ventral tegmental area and the nucleus accumbens; mesolimbic and mesocortical pathways are also involved in the mechanism of nicotine addiction. Bupropion inhibits the reuptake of monoamines and therefore interferes with the reward pathway described above. In addition, it may act antagonistically on nicotinic cholinergic receptors, and this contributes to improved outcomes of anti-nicotine therapy [21, 23].

Bupropion increases the likelihood of successful smoking cessation by 49-72%. This drug may increase the risk of side effects, which will result in discontinuation. The combination of bupropion with other smoking cessation medications, such as varenicline, has been shown to be effective. This combination is associated with an increased likelihood of quitting smoking than monotherapy. Varenicline shows better therapeutic effects than bupropion [24].

An adverse effect of nicotine withdrawal is weight gain. In this case, bupropion shows a beneficial effect in the form of appetite suppression. This is due to the activation of proopiomelanocortin and dopamine agonism in the previously mentioned reward systems [23].

ADHD

Studies are available describing the effects of bupropion in adults with attention deficit hyperactivity disorder despite the lack of such an indication. Bupropion is used in the treatment of ADHD as an alternative to other medications, but its use in this case is debatable. A 2011 review of clinical trials indicated that the drug was safe, while a 2017 review confirmed its effect, but noted at the time the poor quality of the data and poor method of conducting the trials. The 2018 meta-analysis also presents inconclusive information, as doctors assessed bupropion to be beneficial in the treatment of ADHD, while patients did not notice an advantage of bupropion over placebo. Compared to stimulant and non-stimulant drugs, bupropion is less effective [23, 25].

Obesity and overeating

Bupropion in combination with naltrexone is used to treat obesity. Naltrexone is an opioid receptor antagonist and is used to treat opioid dependence. The combination of both drugs was approved for use by the FDA in 2014 as a weight-loss agent for patients with a BMI ≥30 or with a BMI ≥27 and coexisting obesity [22]. The use of bupropion in combination with naltrexone should be considered in obese patients, and especially if they

have co-occurring depression or wish to quit smoking [26]. An additional group of patients in whom such a combination is beneficial are those with overeating disorders, and if the therapy has a positive effect, maintenance treatment with the same drugs should be continued [27].

AGOMELATINE

General information

Agomelatine (AGM) is among the atypical antidepressants used to treat severe depression in adults, and is the first antidepressant to have a component of non-monoaminergic activity. It belongs to the melatonin agonists and selective serotonin antagonists, and additionally acts as a selective agonist of melatonin MT1 and MT2 receptors, as well as a selective antagonist of 5-HT2C/5-HT2B receptors. 5-HT2C antagonism exhibits anti-anxiety effects through activation of GABA neurons in the amygdala, the nucleus accumbens of the striatum and the hippocampus.

AGM is involved in the resynchronization of disturbed diurnal rhythms, which promotes improved sleep patterns, and at the same time, by blocking serotonin receptors, increases the availability of norepinephrine and dopamine in the prefrontal cortex, showing antidepressant effects [28, 29].

Pharmacokinetics

Agomelatine is largely absorbed in the gastrointestinal tract (>75%). The bioavailability of the drug decreases to less than 5% after first-pass metabolism. The main role in metabolism is played by cytochromes CYP450, CYP1A2 and CYP2C9. The main metabolites include inactive hydroxylated and demethylated agomelatine, which are mainly excreted in the urine. Due to the lack of metabolic activity of agomelatine metabolites, the duration of drug activity depends on the parent compound. The average half-life is about 2 h [28, 30].

Indications

In 2009, agomelatine was introduced in Europe for the treatment of major depressive episodes in adults < 75 years of age [29, 30].

Side effects

The main side effects include nausea, headaches and dizziness, as well as migraine headaches, drowsiness and insomnia. Gastrointestinal complaints include diarrhea, constipation, abdominal pain and vomiting. Other reported side effects include hyperhidrosis, back pain, fatigue and anxiety. Laboratory tests may show an increase in aspartate and alanine aminotransferase levels [30].

Sleep

Circadian rhythm sleep-wake disorders (CRSWD) are conditions associated with chronic or recurrent abnormalities in sleep patterns. They mainly result from changes in the functioning of the internal biological clock or its mismatch with external factors regulating sleep timing. An important role in the regulation of the diurnal rhythm is played by the activation of melatonin receptors, which helps synchronize the biological clock [30]. In addition to regulating the diurnal rhythm, agomelatine also increases slow-wave sleep, which reduces depression. A study published in 2024 evaluated the effects of 6-week agomelatine therapy compared to fluoxetine on cognitive function and sleep in people with major depressive disorder. Both drugs had a positive effect on neurocognitive function and sleep parameters in the subjects. Significant improvements were found in verbal and working memory, attention, psychomotor speed and function. Agomelatine proved more effective than fluoxetine in assessing subjective sleep quality on the PSQI and TMT-B. Agomelatine may improve sleep quality better than tricyclic antidepressants in patients with severe depressive episodes [31].

Alzheimer's disease

More than 50 million people worldwide have Alzheimer's disease, with 9 out of 10 patients developing behavioral and psychological symptoms of dementia. Serotonin, acting as a neurotransmitter and neuromodulator, is involved in the regulation of psycho-emotional, sleep and feeding functions. Agomelatine, by acting on serotonin receptors, can alleviate symptoms of depression and anxiety, and this is associated with improvements in patients' lives and functioning. It should also be noted that this drug is not ideal, as it has less evidence of efficacy in elderly patients, and the risk of liver damage may increase [32]. In addition, clinical and experimental animal studies indicate that agomelatine may be a promising

therapeutic option, contributing to simultaneous improvements in memory, sleep quality and cognitive function [33].

Obstructive sleep apnea

A study published in 2023 evaluated the effect of agomelatine on the sleep of patients with obstructive sleep apnea. The randomized trial involving 70 adult patients with the aforementioned condition involved the administration of 50g of the drug one hour before bedtime for 3 noe. The control group did not receive the drug. A comparison of sleep parameters was made. The group of subjects who received agomelatine showed longer sleep time (397 vs. 287.5 min; $p < 0.004$), higher sleep efficiency (75.6% vs. 65.1%; $p < 0.005$) and lower percentage of awakenings (7.5% vs. 8.8%; $p < 0.004$). It can be concluded that agomelatine has a beneficial effect on sleep duration and quality in patients with obstructive sleep apnea [34].

Bowel

Some antidepressants exert anti-cancer effects due to modification of the tumor environment or alteration of the immune response. Colorectal cancer ranks 3rd among the most common cancers worldwide and 2nd in terms of mortality. Current treatment is based on chemotherapy used in mono or polytherapy. Current methods are associated with adverse side effects and the development of chemo-resistance.

A study published in 2023 evaluated the use of agomelatine as an anti-tumor therapy in established colon cell lines in vitro and in vivo in nude mice. The use of antidepressants usually does not cause many side effects. Patients with a cancer diagnosis often require supportive care with antidepressants, so the use of agomelatine may provide a double benefit. In addition, resistance to 5-FU in colorectal cancer patients is associated with non-functional p53. Agomelatine may overcome this barrier, demonstrating efficacy independently of p53, as confirmed in the model used in this study [35].

Conclusions

Amitriptyline, bupropion and agomelatine are drugs used to treat depression, differing in mechanism of action and safety profile, in addition to being used to treat other conditions.

Amitriptyline, a tricyclic antidepressant, is widely used to treat chronic neuropathic pain, fibromyalgia and migraine. With its additional action on muscarinic and histamine H1 receptors, it is also used to treat other conditions.

Bupropion, a norepinephrine and dopamine reuptake inhibitor, is used in the treatment of nicotine addiction, helping to reduce nicotine craving. In addition, it is used in the treatment of ADHD in adults, and, in combination with naltrexone, helps in the fight against excessive weight gain and overeating.

Agomelatine, a melatonin MT1 and MT2 receptor agonist and 5-HT2C receptor antagonist, in addition to depression, may be helpful in regulating diurnal rhythms, making it applicable to sleep disorders, especially in patients with secondary insomnia. It may also have potential benefits in the treatment of anxiety and adaptation to time zone changes.

Each of these drugs has unique properties, allowing them to be used in a wide range of disorders beyond depression.

Disclosure

Authors' contribution

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