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Potential uses of Mirtazapine in palliative care beyond its antidepressant effect

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ABSTRACT

Evaluation and treatment of psychiatric disorders is crucial in palliative care patients at the end of life. Depression and anxiety disorders are highly prevalent and should not have been taken as normal in palliative care patients, as they are associated with decreased quality of life and increased morbidity and mortality. The pharmacological treatment of these disorders include selective serotonin reuptake inhibitors and tricyclic antidepressants that should not be the most suitable options because adverse effects and drug interactions associated with them. One of the drugs that is not used often in these contexts is Mirtazapine. Mirtazapine is an approved drug for the treatment of depression that has proven to have a faster onset of action and greater effectiveness than several other antidepressants. Its mechanism of action is distinctive because alpha2 adrenergic receptor antagonism and 5-HT2a-c receptor antagonism are the main antidepressant mechanisms without involving inhibition of the serotonin transporter. It is also active as an antagonist of histamine 1 and 5-HT3 receptors which produce its hypnotic-sedative, antiemetic and orexigenic properties. Its noradrenergic and serotonergic mechanism also has effects on chronic pain. These factors may be potentially useful in patients treated in palliative care units and could also reduce polypharmacy or the use of drugs that are likely to generate undesirable adverse effects. The purpose of this review is to show evidence of this drug's use in various contexts related with palliative care patients, mainly those at the end of life, and to establish their safety profile in comparison with typically used antidepressants.

Key words: Mirtazapine, pain, antidepressant, palliative.

RESUMEN

La evaluación y el tratamiento de los trastornos psiquiátricos son cruciales en los padecimientos al final de la vida. La depresión y los trastornos de ansiedad son altamente prevalentes y no deben ser tomados como parte de la normalidad en los pacientes en cuidados paliativos, ya que están asociados a disminución de la calidad de vida, así como mayor morbilidad y mortalidad. Las herramientas de tratamiento farmacológico de estos padecimientos incluyen a los antidepresivos tricíclicos o a los inhibidores selectivos de la recaptura de serotonina que pudiesen no ser los más adecuados por sus efectos adversos e interacciones medicamentosas. Uno de los fármacos que se ocupa relativamente poco en estos contextos es la mirtazapina. La mirtazapina es un fármaco aprobado para el tratamiento de la depresión que se ha probado tiene un inicio de acción más rápido y mayor efectividad que diversos otros antidepresivos. Su mecanismo de acción es distintivo, pues tiene al antagonismo del receptor alfa-2 adrenérgico y el antagonismo del receptor 5-HT2a y c como sus principales actividades sin involucrar a la inhibición del transportador de serotonina. Además cuenta con el bloqueo del receptor 1 de histamina y del receptor 5-HT3 dentro de sus afinidades que le proporcionan actividad como hipnótico-sedante, antiemético y orexigénico. Por su mecanismo noradrenérgico y serotoninérgico también tiene efectos sobre el dolor crónico. Estos factores pueden ser potencialmente útiles en los pacientes tratados en unidades de cuidados paliativos y generarían una reducción de la polifarmacia o del uso de

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fármacos que pudiesen generar efectos adversos indeseables en esta población. Esta revisión tiene la finalidad de presentar la evidencia del uso de este fármaco en diversos contextos relacionados con la atención de los pacientes en cuidados paliativos, principalmente aquellos que se encuentran al final de la vida, así como establecer su perfil de seguridad en comparación con los antidepresivos clásicamente utilizados.

Palabras clave: Mirtazapina, dolor, antidepresivo, paliativos.

INTRODUCTION

Mirtazapine is a piperazino-azepine molecule synthesized in 1989 which has been approved by the European Union for treating Major Depressive Disorder since 1994, and since 1996 in the United States. It is a distinctive type of antidepressant that has been described as noradrenergic and specific serotonergic, unique in its class (1). Mirtazapine does not inhibit the serotonin transporter (SERT), or other monoamines, as its main action mechanism as selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenaline reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs).

The use of SSRI, SNRI and TCA antidepressants, although they are effective and easily tolerated, offer a pharmacological profile that may not be suitable in cases of patients with painful pathologies or in end-of-life palliative care. SSRI treatments often offer disadvantages in pharmacological interactions with other drugs commonly prescribed by palliative care physicians such as with antiepileptic drugs, Carbamazepine or Phenytoin, with opioid or non-opioid analgesics or antimicrobial drugs. Commonly prescribed antidepressants also present a profile of adverse effects that may lead to abandoning treatment.

The treatment of psychiatric comorbidity is a high-priority in patients in palliative are, especially those at the end of life. The existence of psychiatric pathology in such patients causes a reduction in quality of life (2) and is associated with low therapeutic adherence (3), risk of suicide (4) and poorer results for principal therapy (5) or in somatic variables, such as bone density (6). The goal of palliative care is to alleviate the patient's suffering and improve their quality of life by focusing on the whole patient in their physical, psychological, spiritual and social environment. Treatment of psychiatric suffering is therefore also part of palliative care. At the same time, there exist a number of psychiatric symptoms and syndromes associated to non-psychiatric medical conditions that require treatment and which may give rise to polypharmacy. This aspect has been associated with health alterations and risks such as events related with medication, falls, delirium, hospitalizations, and greater morbidity and mortality (7-9). For this reason, it is desirable to use broad-spectrum drugs for a variety of ailments with effectiveness and which in turn, offer an adequate safety profile for the different pathologies described.

A drug that may combine these characteristics is Mirtazapine. Owing to its pharmacological profile and pharmacokinetics, its prescription to patients in palliative care provides advantages that would allow a reduction in polypharmacy while improving quality of life. The goal of this article is to underline these advantages on the basis of the evidence available.

PHARMACOLOGICAL PROPERTIES OF MIRTAZAPINE

Mirtazapine is a potent antagonist at 5-HT2a-c, 5-HT3 serotonin and Alpha-2 adrenergic receptors in a central role. This last of these is considered to be its main mechanism, causing the greatest action liberating serotonin and noradrenaline, because the Alpha-2 receptor acts as an "autoreceptor" in the soma of the presynaptic neuron, which blocks the release of monoamines. The fact that it is antagonistic at 5-HT2a-c and 5-HT3 receptors brings about a more selective serotonergic transmission to 5-HT1 receptors, which, it would seem, stimulates an improvement in mood. Blocking these receptors generates a reduction in the adverse effects commonly reported for SSRI, SNRI and TCA antidepressants such as nausea, sexual dysfuntion or dizzinness. It also has major antagonistic properties at the histamine H1 receptor; this property together with antagonism at the 5-HT2a receptor can improve sleep and make it refreshing, as well as increasing appetite along with blockage of the 5-HT2c receptor. Blocking the 5-HT2a-c and 5-HT3 receptor can also lead to an increase in the release of monoamines at prefrontal level. Mirtazapine lacks major affinities with other receptors and, unlike many antidepressants, does not offer activity as an antagonist on the serotonin transporter (1).

Mirtazapine is absorbed through the gastrointestinal tract without the presence of food affecting its bioavailability. It presents 85% binding to plasma proteins. It is metabolized through the cytochrome p450 system in isoforms 1A2, 2D6 and 3A4. It has a half life of 20 to 40 hours. It is excreted mainly by urine (75%) and the rest by faeces. Accordingly, clearance can be affected in the event of liver or kidney ailments, a situation that requires adjustment of dosage (1).

EFFECTIVENESS IN TREATING MAJOR DEPRESSIVE DISORDER

Depression is a syndrome characterized by deep, disabling sadness, loss of pleasure or interest in most activities, alterations in appetite that lead to weight loss or gain beyond what may be explained by non-psychiatric medical suffering, sleep alterations such as insomnia or hypersomnia, psychomotor delay or agitation, tiredness, feelings of uselessness or excessive blame, a reduction in the ability to concentrate and even suicidal thoughts and behavior (10). This condition can be found in a high proportion of patients in palliative care, bearing in mind that up to 25% of cancer patients report it (11), between 20% and 50% of patients who receive hemodyalisis (3,12) and between 13% and 25% of patients who are attended in palliative care units for different ailments (13). Depression should not be considered as something normal in patients in palliative care, especially those at the end of life, or to be a syndrome that all patients report. Although sadness and grieving are reactions to be expected, and their individual management depends on the confrontation mechanisms that people have developed, depression is a psychiatric medical condition that requires specific treatment and which, if not dealt with as such, involves major loss in quality of life and general health, always involving the possibility of suicide. A major line of research has related depression with mortality among cancer patients. A met-analysis evaluates that cancer patients diagnosed with depression show less favorable results than those without this diagnosis (14), and another study demonstrates that among patients with oropharyngeal cancer, depression is associated with a shorter survival term but also with the illness's recurrence (15).

Since the first placebo-controlled studies carried out to approve Mirtazapine for treating major depressive disorder and anxiety disorders, Mirtazapine has presented remarkable effectiveness when compared with the placebo (16). Nevertheless, maybe it is more interesting that this molecule has shown superiority above other drugs. One of the articles most quoted regarding the effectiveness and acceptability of antidepressants is the study by Cipriani et al. (17), which reported that almost all the existing antidepressants are equally effective except for Mirtazapine, Escitalopram, Venlafaxine and Sertraline, which have greater effectiveness in reducing scores on diagnostic depression scales by, at least, 50% in the course of eight weeks, compared with Fluoxetine and the rest of antidepressants. As regards acceptability, measured by the number of patients who abandoned treatment before the study term, for any reason, Mirtazapine had acceptance similar to Fluoxetine.

Mirtazapine is also applied as a reinforcement strategy. As a consequence of its mechanism of action different to serotonin reuptake, it may be used synergically with selective serotonin reuptake inhibitors or with tricyclic antidepressants. In the study by Fava et al., in which 377 patients with failed treatment to achieve remission with the antidepressant citalopram were recruited, the change or reinforcement with Mirtazapine or Nortripyline was evaluated. Although the results were lesser for patients treated with Mirtazapine (12.3 vs. 19,8% for nortriptyline) they did not differ statistically. Nevertheless, we should highlight the fact that although it did not reach statistical significance, the result was that Mirtazapine had a shorter response time (5.7 weeks vs. 6,3 weeks) (18).

Adequate effectiveness has been reported when this drug is used in hospital contexts. When Mirtazapine use is compared with Venlafaxine in a hospital context, it has been shown to have faster response time, a lower number of adverse effects and a larger number of patients in remission, although it does not achieve statistical significance (19).

EFFECTIVENESS ON ANXIETY DISORDERS

Anxiety disorders are more prevalent among the population than depression and, frequently, are much less acknowledged, and therefore treated (20). The palliative care population is not unrelated to this. Different studies have shown that, approximately, between 9% to 18% of patients with cancer suffer from some kind of anxiety disorder that may bring about a more significant decrease in their quality of life (2,21). These disorders also appear with prevalence in other ailments with palliative care. For example, a study in a hemodialysis center in the United States showed that 45% of patients in this treatment modality presented some type of anxiety disorder (22).

The evidence does not consistently support the use of Mirtazapine in anxiety disorders. There are studies that support its use (23,24) while others do not (25). The greatest evidence backs its use in cases of patients with mood disorders and comorbid anxiety symptoms (26-29). For this reason, in several treatment guides, Mirtazapine appears as a second option, subsequent to the use of selective serotonin uptake inhibitors (30,31).

Perhaps its greatest utility regarding anxiety is in reducing polypharmacy and in treating other symptoms associated with the anxiety-depression binomial, such as appetite and sleep alterations. Nevertheless, Mirtazapine

has been associated with an improvement in anxiety precisely in palliative care patients. In a study with 53 cancer patients diagnosed with major depressive disorders, anxiety disorder or adaptive disorder, were randomized to take Mirtazapine, Imipramine or placebo and evaluated at six weeks in a a double-blind design. Patients who took Mirtazapine improved significantly in the evaluation of anxiety compared with Imipramine or placebo (32).

EFFECTS ON INSOMNIA

Mirtazapine's main affinity focuses on the type-1 histaminergic receptor, at which it acts as an antagonist. To date, four histaminergic receptors have been identified, with receptor 1 involved in the central nervous system (33). Histaminergic neuronal pathways run mainly through the lymbic system in mamillary bodies whose connections with the fornix form a synapsis with the hypothalamus in the tuberomamillary nucleus. The histamine released through these pathways promotes insomnia by inhibiting GABAergic neurons of the ventrolateral preoptic area of the hypothalamus. The histamine action is terminated by histamine N-methyltransferase and its release is stopped by the same histamine in H3 receptors (34). For this reason, classic antihistamines are associated with sedation, considering this an adverse effect. However, in the case of Mirtazapine, this may be an advantage in the case of patients in palliative care.

Physicians must recognize insomnia not only in terms of the traditional optic of difficulty to fall asleep, but rather following the difficulty stay asleep, early awakening or the feeling of non-restorative sleep, the last of which is mostly associated with anxiety disorders. Insomnia, on the other hand, is associated during daytime activity with fatigue, drowsiness, cognitive alterations such as memory, attention and concentration, mood alterations like irritability, sadness, anxiety and even physical symptoms such as migraines (10,34).

Normally, classic treatment for insomnia has been by using benzodiazepines. However, chronic use of these drugs is associated with a number of short-term problems such as daytime sedation in the case of long-acting benzodiazepines such as diazepam or clonazepam, morning "hangover effect" and difficulty in waking up in the case of intermediate-acting drugs,such as alprazolam or lorazepam, difficulty staying asleep in the the case of short-acting or ultra short-acting drugs like Estazolam or Triazolam, mainly used on geriatric patients with the subsequent risk of fractures, delirium and other comorbidities (35,36). Conversely, benzodiazepines generate sedation thanks to their GABAergic agonism, reducing latency time to initiation of sleep and the number of awakenings, with the setback that they also reduce total slow wave sleep (3 of sleep) and rapid-eye-movement, increasing the total time of stage 2 sleep (light sleep), as well as REM latency, that is, subjects who take benzodiazepines take longer to reach REM sleep and spend more time in light sleep (1). In the long term,the use of benzodiazepines has been primarily associated with physical dependence and other associated psychiatric disorders such as dementia (37), mood or anxiety disorders (10), and other conditions like urinary incontinence (38) and even an increase in mortality (39). For these reasons, benzodiazepines have been replaced by other options as first-line drugs in treating insomnia in a number of treatment guides (40).

Mirtazapine, by offering H1 antagonism, generates sedation by the mechanism explained above. However, it may be more interesting to underline another of its antagonisms, the 5-HT2c receptor. Pure antagonists of this receptor, such as Ketanserin and Ritanserin, promote an increase in slow-wave sleep time. This sleep stage is the one associated with rest (41).

In polysomnography studies with healthy volunteers, taking Mirtazapine has been associated with a reduction in total stage-1 sleep-time (light sleep), an increase in total sleep time, in slow-wave sleep-time and REM sleep-time, as well as an increase in the efficiency of sleep (the proportion of total sleep time between total time in bed, expressed as a percentage) and a reduction in the number and duration of night-time awakenings (42,43).

Applied to patients in palliative contexts, Mirtazapine improves sleep-related variables. In the abovementioned Cankurtaran study, cancer patients who took Mirtazapine, apart from improving in terms of anxiety with respect to Imipramine or placebo, showed a significant change in sleep variables (32). In a similar study carried out by Kim, 42 cancer patients took Mirtazapine for four weeks in an open design. In the sleep variables studied, there were significant differences (total sleep time, subjective sleep quality, ease of morning awakening, behavior following awakening and measurement of insomnia on the Montgomery-Asberg depression rating scale). These changes in sleep correlated positively with a reduction in scores for anxiety and depression (44).

EFFECTIVENESS OF MIRTAZAPINE ON APPETITE

One of the adverse effects that often limits the use of Mirtazapine, especially in younger patients or those with metabolic syndrome, is its effect on appetite. Antagonism at the H1 receptor and at the 5-HT2a and 2c receptor has been related with the presence of overeating and obesity with the subsequent increase in insulin resistance (34).

Although this is a limiting adverse effect for some populations, it may be an advantage for palliative care patients. Anorexia and weight-loss is associated with a reduction in quality of life and a decrease in the survival rate of cancer patients (45). In heart-failure patients, appetite loss is related with age, cognitive function, insomnia and depressive symptoms. Among this population, the poor appetite that generates low weight and malnutrition is associated with a negative diagnosis (46). Accordingly, it is important among patients in such conditions to maintain appropriate nutritional control, a situation that is compromised by anorexy.

Mirtazapine has been tested for these conditions in older adults (47) and in cancer patients (48, 49), where it improves appetite, weight and, therefore, quality of life.

EFFECTS OF MIRTAZAPINE ON NAUSEA

Another of Mirtazapine's major antagonisms focuses on the 5-HT3 receptor. This receptor is the only inotropic serotoninergic receptor and is located in different parts of the brain, mainly in the entorhinal cortex and in the brain stem. Its activity is associated with the release of dopamine at a mesolimbic level and a decrease in acetylcholine. In the brain stem, the activity of these receptors is related with central-origin vomiting and with nausea, while it also generates an increase an increase in intestinal motility (33,34).

Mirtazapine has an affinity to this receptor very similar to Ondansetron, which is classically used for treating chemotherapy or postoperative nausea and vomiting. Thompson reports effectiveness on anorexy and nausea secondary to chemotherapy or radiotherapy in a series of cases regarding patients with gynecological cancer (eight patients with breast cancer, six with cervical cancer, five with ovarian cancer and one patient with uterine cancer) (49). In the above-mentioned article by Kim, one of the most remarkable effects in the use of Mirtazapine focused on the reduction in nausea, with this change most significant in patients who had chemotherapy.

This effect appeared as from the medicine's first dose (44).

EFFECTS OF MIRTAZAPINE ON CHRONIC PAIN

The association of serotoninergic and noradrenergic drugs with an improvement in chronic pain is well studied. A number of antidepressants, such as some tricyclic drugs (for example Amitriptyline), and combination drugs, such as Duloxetine, are approved for treating conditions that involve this kind of pain, such as phantom limb pain, diabetic neuropathy or fibromyalgia.

Mirtazapine has serotoninergic and noradrenergic mechanisms, because it is an an antagonist of the Alpha-2 adrenergic receptor. At central level, this receptor is a "self-receptor" of noradrenaline and serves to reduce serotoninergic and noradrenergic transmission, so its blockage leads to an increase in the release of both neurotransmitters (1). This suggests that Mirtazapine has a potential role in treating chronic pain, mainly of a neuropathic type. This effect was demonstrated in the study by Arnold et al., where healthy volunteers were randomized to take a placebo or 30 milligrams of Mirtazapine in a pain paradigm that used stimulation of the sural nerve, using a cross-over design. Patients taking Mirtazapine showed an increase in pain tolerance (50) (50).

Mirtazapine has proven to be relatively effective in some chronic pain complaints, such as irritable bowel syndrome, fibromyalgia, tension-type headache and migraine (51). However, focusing on palliative patients, attention is drawn to two case reports and a clinical trial. According to the report by Christodolou, the use of Mirtazapine is associated with a reduction in pain intensity in a patient with post-herpetic neuralgia as from the first dose of 15 mg (52). Kuiken reported four cases of patients with phantom limb syndrome who, after taking Mirtazapine, over several weeks of treatment reported a reduction by at least 50% in pain intensity (53). Finally, Nishihara et al. studied different interventions in order to reduce pain secondary to bone metastases in 37 cancer patients who were randomized in three groups: a) 150 mg/d Pregabalin, b) 75 mg Pregabalin with 15mg/d Mirtazapine and c) 75 mg/d Pregabalin with 10 mg/d Imipramine. Patients in group b and c showed an equivalent reduction in the total intensity, but it was significant that the patients with Mirtazapine showed a faster response in reducing episodes of paroxysmal pain as from the first day, which was statistically relevant with respect to only using

Pregabalin or with Imipramine. Subsequent to day three, the effect of the combination with Imipramine was equaled in effect, but the Mirtazapine group always showed a greater effect than the group that only used Pregabalin (54).

PRECAUTIONS IN PALLIATIVE PATIENTS

Although Mirtazapine has a broad safety profile, there exist a number of adverse effects that should be taken into account especially in pharmacological interactions. Owing to its pharmacodynamic profile, Mirtazapine produces sedation with greater frequency than other antidepressants. As a result, it is important to determine how other drugs prescribed to the patient can generate these symptoms to avoid a summation effect. Examples of these are the benzodiazepines, tricyclic antidepressants, phenothiazines, first and second-generation anti-psychotics, anticonvulsivants and analgesic opioids (1). It is also important to consider drugs that can generate increases in serotonin concentrations due to the possibility of serotoninergic syndrome. Particular care should be taken with drugs that have a monoamine oxidase inhibitor mechanism, such as the antibiotic Linezolid, or which generate serotonin reuptake inhibition, such as Tramadol or Methadone (55).

Although Mirtazapine is associated with a substantial improvement in sleep, special care should be taken with patients prescribed dopamine antagonist drugs, such as antipsychotics, or patients where dopamine transmission is compromised, such as Parkinson's disease or Lewy body dementia, because Mirtazapine causes, with greater frequency than other antidepressants, the dyssomnia known as restless leg syndrome, characterized by the urgent need to move legs or arms, mainly in situations at rest, and which is alleviated partially by movement. This syndrome is associated with deficits in dopaminergic transmission and is treated with dopaminergic agonists, such as Ropirinole or Pramipexole (56,57).

Finally, Mirtazapina can cause constipation due to its antagonism with the 5-HT3 receptor. Accordingly, it is important to take special care with persons who suffer from conditions in which constipation could be especially dangerous, in cases of bleeding in the lower gastrointestinal tract, colorectal cancer or patients following surgergy for colostomy, and the use of drugs that reduce intestinal motility in other ways, such as analgesic opioids, non-steroid analgesics, other antiemetics, antispasmodics, tricyclic antidepressants or other drugs with an anticholinergic effect, such as some chemotherapies carried out with Vinca alkaloids (34).

CONCLUSIONS

Mirtazapine is a drug that has potential advantages in treating patients in palliative care, especially those at end of life, while offering a broad safety margin. Beyond its effects as a highly effective antidepressant and with faster onset of action than those used traditionally, it provides a number of effects thanks to its unique profile of affinity with different receptors, which have been demonstrated in non-psychiatric patients under hospital conditions, and even in palliative care. Careful use of this drug, taking into consideration pharmacological interactions that may be harmful or conditions where a relative contraindication could exist, in addition to monitoring its effects, could reduce the need for several drugs and significantly improve quality of life for these end-of-life patients.

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CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

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