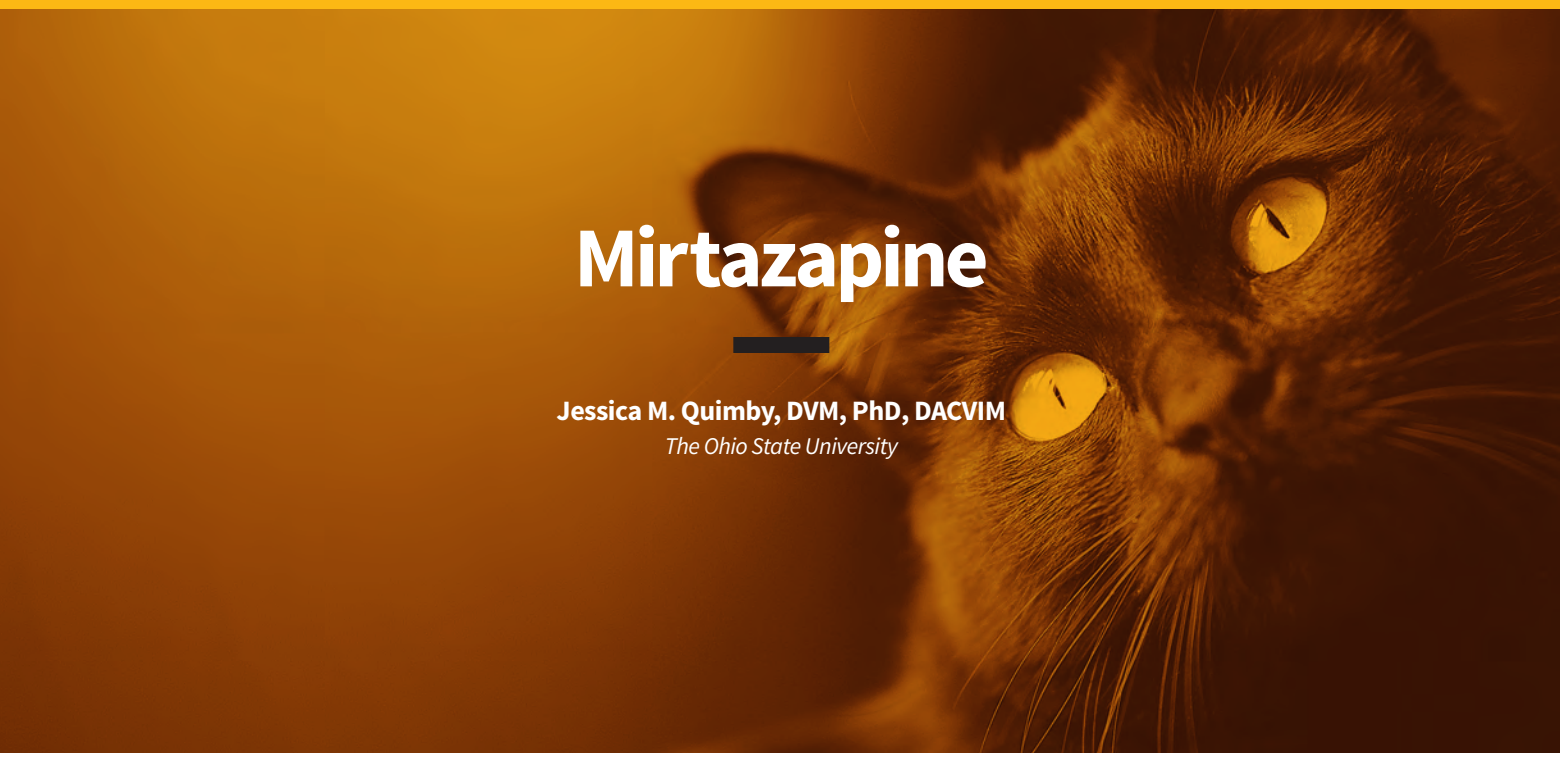

Mirtazapine

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Mirtazapine has become widely used in veterinary medicine due to its commonly recognized effects of appetite stimulation and weight gain.

CLINICAL APPLICATIONS

- Mirtazapine is an effective appetite stimulant in cats[1-5] and is used for nutritional support in both dogs and cats with acute and chronic illness.
  - Mirtazapine has been demonstrated in placebo-controlled trials to result in appetite stimulation in normal cats and appetite stimulation, weight gain, and improved body condition in cats with chronic kidney disease (CKD).[3,4]
  - The drug's mechanism of action is not fully understood but likely involves antagonism of the serotonin 2C ($5HT_{2c}$) receptor, which is known for its appetite-inhibition activity, as well as antagonism of the histame 1 (H_1) receptor, which also plays a role in appetite regulation.[6,7]
- Mirtazapine has antiemetic properties due to its antagonism of the serotonin 3 ($5HT_3$) receptor and has been shown to decrease vomiting in cats with CKD.[4]
- Because of its superior receptor-binding affinity, there is some evidence that concurrent administration of mirtazapine with $5HT_3$-receptor antagonists (eg, ondansetron) may decrease the efficacy of ondansetron in humans.[8]
  - Although evidence for this interaction is not available for cats and dogs, this phenomenon should be taken into account when choosing antiemetic and antinausea regimens.
- Mirtazapine appears anecdotally to have some appetite-stimulating properties in dogs, but no studies have been conducted to assess appetite in healthy or hyporexic dogs receiving this drug.[9,10]
- A prokinetic effect has been demonstrated in healthy dogs that received mirtazapine at 1.7-2.0 mg/kg PO once, resulting in improved gastric emptying and colonic motility.[11]
  - The clinical utility of this prokinetic effect merits further investigation.

PHARMACOKINETICS & PHARMACODYNAMICS

- In cats, administering one-fourth of a 15-mg tablet (3.75 mg) every 3 days was initially recommended based on an early, mostly anecdotal, open clinical trial in which a dose was extrapolated from use in humans[10]; however, several studies have since helped determine a more appropriate starting dose for cats.
- Mirtazapine is amenable to transdermal administration and has been demonstrated to achieve therapeutic serum concentrations in cats.[1,5]

- Placebo-controlled pharmacodynamic studies have demonstrated that transdermal administration of mirtazapine results in increased appetite in normal cats and increased appetite and weight in cats with CKD.[1,5]
- Transdermal mirtazapine obtained from compounding pharmacies can have high variability[1] among preparations and may not have the same stability and efficacy as that demonstrated in referenced studies.

▸ The pharmacokinetics of mirtazapine is affected by age and several disease states.

- As compared with humans (half-life, 20-40 hours), the half-life of oral mirtazapine in young normal cats is relatively short (9.2 hours).
- A repeat-dosing study demonstrated little drug accumulation with daily administration of 1.87 mg/cat in young cats[2,3]; median peak serum concentrations were reached in one hour.
- In contrast, the half-life of oral mirtazapine is prolonged in elderly cats (12.1 hours) and cats with CKD (15.2 hours) and/or liver disease (15.1 hours).[2,12]
  - This is similar to pharmacokinetics in humans in which kidney and/or liver disease prolong half-life by 25% to 30%.[13]

▸ In young healthy dogs, the half-life of mirtazapine is 6 hours, with peak serum concentration at 0.9 hours.[9]

ADMINISTRATION & DOSE INTERVAL

▸ The variable pharmacokinetics of mirtazapine should be taken into account when determining the dose interval.

▸ The suggested oral dose interval for cats is 1.87 mg/cat PO q24h in younger cats with normal organ function, q48h in cats with CKD, and q48-72h in cats with liver disease.[2,3,12]

- A higher dose of 3.75 mg has been associated with increased side effects, typically without any greater efficacy for appetite stimulation.[3,14]
  - Some cats may require titration up to this dose.[3,14]

▸ The suggested (anecdotal) dose interval for dogs is 0.6-1.0 mg/kg q12h.

- Studies evaluating dose interval in dogs with liver and/or kidney disease have not been conducted.[9]

SAFETY & ADVERSE EFFECTS

▸ Adverse effects in cats are dose-dependent and much more likely to occur at higher doses or with accidental administration of an entire 7.5- or 15-mg tablet.[3,14]

- Adverse effects, which appear to be more common in cats than in dogs, most commonly include vocalization, agitation, vomiting, abnormal gait/ataxia, restlessness, tremors/trembling, hypersalivation, tachypnea, tachycardia, and lethargy.[3,14]
- With both the oral and transdermal formulations, the dose should be titrated to the lowest effective amount for appetite stimulation to minimize adverse effects.

▸ Subclinical reversible increases in liver enzymes (eg, marked increases in alanine transaminase [possibly idiosyncratic]) may occur as a result of mirtazapine administration; discontinuation of the drug is recommended in these patients.[4]

▸ Concurrent administration with selective serotonin reuptake inhibitors may increase serotonin syndrome-like adverse effects.[13]

CKD = chronic kidney disease

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